OBSERVATIONS IN REPLY

PATENT:

European Patent No:	1141274
Title:	Soluble Receptor BR43x2 and Methods of Using them for Therapy
Patent Proprietor:	ZymoGenetics, Inc.

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CONTENTS

1 INTRODUCTION

1.1 The Patent Proprietor (henceforth "The Proprietor") hereby files its Observations in Reply to the Oppositions filed by Opponents I-IV.

2 REQUESTS

2.1 The Proprietor requests that all four Oppositions be refused.

2.2 The Proprietor requests that those parts of the Oppositions in which the Patent is opposed on the ground of un-Patentability under Article 52(4) EPC (Article 100a EPC) be refused.

2.3 The Proprietor requests that those parts of the Oppositions in which the Patent is opposed on the ground of lack of novelty under Article 54 EPC (Article 100a EPC) be refused.

2.4 The Proprietor requests that those parts of the Oppositions in which the Patent is opposed on the ground of lack of inventive Step under Article 56 EPC (Article 100a EPC) be refused.

2.5 The Proprietor requests that those parts of the Oppositions in which the Patent is opposed on the ground of insufficiency of disclosure under Article 83 EPC (Article 100b EPC) be refused.

2.6 The Proprietor requests that those parts of the Oppositions in which the Patent is opposed on the ground of added matter under Article 123(2) EPC (Article 100c EPC) be refused.

2.7 The Proprietor hence requests maintenance of the Patent as per the granted Claims 1-38 (Main Request).

2.8 In the event that the Opposition Division decides not to maintain the Patent as per the granted Claims 1-38 (Main Request), the Proprietor requests maintenance of the

Patent as per the amended set of Claims 1-70 filed herewith (Auxiliary Request 1).

2.9 The Proprietor requests the opportunity to file one or more further sets of amended claims (ie. Further Auxiliary Request claim sets) during the course of proceedings.

2.10 The Proprietor requests Oral Proceedings in the event the application is not to be granted as per the Main Request or Auxiliary Request 1.

3 BRIEF SUMMARY OF THE OPPOSITIONS

3.1 Opponent I (Corixa Corporation) has opposed the Patent as a whole. The opposition is based on the grounds of lack of novelty, lack of inventive step, lack of sufficiency of disclosure and added matter.

3.2 Opponent II (Human Genome Sciences) has opposed the Patent as a whole. The opposition is based on the grounds of lack of novelty, lack of inventive step and lack of sufficiency of disclosure.

3.3 Opponent III (Genentech, Inc.) has opposed the Patent as a whole. The opposition is based on the grounds of lack of novelty, lack of inventive step, lack of sufficiency of disclosure and added matter.

3.4 Opponent IV (Biogen Idec Inc.) has opposed the Patent as a whole. The opposition is based on the grounds of lack of novelty, lack of inventive step and lack of sufficiency of disclosure.

4 MAIN REQUEST (CLAIMS 1-38 AS GRANTED)

Novelty - Article 54 EPC

4.1 Independent "use" Claims 1 and 3 of the patent as granted (and hence all claims dependent thereon) are novel over the prior art cited by Opponents I-IV, which fails to disclose the specific mechanism of action of the recited compounds. In more detail, none of the cited prior art discloses using the recited compounds to inhibit ztnf4 activity or to inhibit BR43x2, TACI or BCMA receptor-ztnf4 engagement.

4.2 Product *per se* Claims 29-35 are directed towards BR43x2, which is not disclosed in any of the cited prior art. Hence, Claims 29-35 are novel over the cited prior art.

4.3 The prior art cited by Opponents I-IV fails to disclose any antibodies that specifically bind to the polypeptide sequences recited in Claim 36. Hence, pharmaceutical composition Claim 36, and dependent Claims 37-38, are also novel.

Inventive Step – Article 56 EPC

4.4 There is no suggestion in the cited prior art of the specific mechanism of action of the compounds recited in Claims 1 and 3 of the patent as granted. In particular, only a limited number of the cited prior art documents refer to ztnf4, and none of these documents suggests any link between inhibition of ztnf4 activity/ engagements and any of the compounds recited in Claims 1 and 3. Thus, "use" Claims 1-28 of the patent as granted are inventive over the prior art cited by Opponents I-IV.

4.5 As discussed in more detail below with regard to Auxiliary Request 1, Claims 29-35 of the patent as granted would not be obvious to a skilled person in the light of the cited prior art. None of the cited documents provides any suggestion of the specific BR43x2 polypeptides of SEQ ID NOs: 2 and 4, or polynucleotide sequences of SEQ ID NOs: 1 and 3, and hence Claims 29-35 are inventive.

4.6 There is no suggestion of the pharmaceutical compositions of Claims 36-38 in the cited prior art, since there is no suggestion of any of the recited specifically-binding

antibodies in the cited prior art. In particular, as discussed above, SEQ ID NOs: 2 and 4 were not known prior to the present application, and hence it would not have been obvious to raise an antibody against these sequences.

Sufficiency of Disclosure – Article 83 EPC

4.7 We would refer the Opposition Division to our detailed comments, below, with regard to Auxiliary request 1.

Added Matter – Article 123(2) EPC

4.8 We would refer the Opposition Division to our detailed comments, below, with regard to Auxiliary request 1.

5 BASIS FOR AUXILIARY REQUEST 1 – Article 123(2)&(3) EPC

Article 123(2) & (3) EPC

5.1 According to Article 123(2) EPC, a European Patent application or a European Patent may not be amended in such a way that it contains subject-matter that extends beyond the content of the application as filed.

5.2 According to Article 123(3) EPC, the claims of a European Patent may not be amended during opposition proceedings in such a way as to extend the protection conferred.

Written basis for amended Claims 1-55

5.3 Amended Claim 1 has basis in Claim 1 of the Patent as granted. In more detail, parts a), b), c), d), e), f), and g) correspond to parts a), e), f), i), k), m) and n) of Claim 1 of the Patent as granted, respectively. New parts h) and i) of Claim 1 have basis in parts m) and n) of Claim 1 of the Patent as granted, which provide the upper and lower limits of the newly claimed ranges (T2/81).

Claim 1 has been further amended by insertion of a list of defined medical conditions for which the claimed medicament is useful. Basis for asthma, bronchitis, emphysema and end stage renal failure is in Claim 19 of the Patent as granted. Basis for renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for inflammation is in Claim 27 of the Patent as granted. Basis for inhibiting antibody production associated with an autoimmune disease is in Claims 16 and 17 of the Patent as granted. Basis for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation is in Claims 22-25 of the Patent as granted.

5.4 Claim 2 is unamended.

5.5 Claim 3 has basis in Claim 3 of the Patent as granted. In more detail, parts a)- d) of

amended Claim 3 have basis in parts a), e), f) and i) of Claim 3 of the Patent as granted, and parts g)- j) of amended Claim 3 have basis in parts k), l), n), and o) of Claim 3 of the Patent as granted. Parts e) and f) of amended Claim 3 have basis in the description, page 31, paragraphs 0185-0186, of the Patent as granted. Parts k) and l) of amended Claim 3 have basis in parts n) and o) of Claim 3 of the Patent as granted, which provide the upper and lower limits of the newly claimed ranges (T2/81).

Amended Claim 3 also recites a list of medical conditions disclosed in the specification as filed that are treatable using the claimed medicament. Basis for these conditions is exactly as given with respect to amended Claim 1 (above).

5.6 Amended Claim 4 has basis in Claim 4b) of the Patent as granted.

5.7 Amended Claim 5 has basis in Claim 5 of the Patent as granted.

5.8 Amended Claim 6 has basis in Claim 6a) of the Patent as granted.

5.9 Amended Claim 7 has basis in Claim 7a) of the Patent as granted.

5.10 Claims 8-12 are unamended.

5.11 Amended Claim 13 has basis in Claim 18 of the Patent as granted.

5.12 Amended Claim 14 has basis in Claim 20 of the Patent as granted.

5.13 Amended Claim 15 has basis in Claim 26 of the Patent as granted.

5.14 Amended Claim 16 has basis in Claim 28 of the Patent as granted.

5.15 Amended Claims 17-23 correspond to Claims 29-35 of the Patent as granted, and are unamended.

5.16 Amended Claim 24 has basis in Claim 36 of the Patent as granted. In more detail,

parts a)-c) of amended Claim 30 correspond to parts a), b) and e) of Claim 36 of the Patent as granted.

5.17 Claims 25 and 26 correspond to Claims 37 and 38 of the Patent as granted, and are unamended.

5.18 Amended Claim 27 has basis in part b) of Claim 1 of the Patent as granted. Claim 27 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for asthma, bronchitis and emphysema is in Claim 19 of the Patent as granted. Basis for nephritis and pyelonephritis is in Claim 20 of the Patent as granted. Basis for renal neoplasms, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for Crohn's Disease is in Claim 26 of the Patent as granted. Basis for inflammation associated with joint pain, swelling or septic shock is in Claim 28 of the Patent as granted.

5.19 Amended Claim 28 has basis in part c) of Claim 1 of the Patent as granted. Claim 28 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for systemic lupus erythematosis, myasthenia gravis, multiple sclerosis and rheumatoid arthritis is in Claim 18 of the Patent as granted. Basis for asthma, bronchitis, emphysema and end stage renal failure is in Claim 19 of the Patent as granted. Basis for renal neoplasms, multiple myelomas, light chain neuropathy or amyloidosis is in Claim 21 of the Patent as granted. Basis for inflammation associated with joint pain, swelling, anaemia or septic shock is in Claim 28 of the Patent as granted. Basis for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation is in Claims 22-25 of the Patent as granted.

5.20 Amended Claim 29 has basis in Claim 1d) of the Patent as granted. Claim 29 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for treating asthma, bronchitis and emphysema is in Claim 19 of the Patent as granted. Basis for nephritis and pyelonephritis is in Claim 20 of the Patent as granted. Basis for renal neoplasms, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for Crohn's Disease is in Claim 26 of

the Patent as granted. Basis for inflammation associated with joint pain, swelling or septic shock is in Claim 28 of the Patent as granted.

5.21 Amended Claim 30 has basis in Claim 1g) of the Patent as granted. Claim 30 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for asthma, bronchitis and emphysema is in Claim 19 of the Patent as granted. Basis for nephritis and pyelonephritis is in Claim 20 of the Patent as granted. Basis for renal neoplasms, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for Crohn's Disease is in Claim 26 of the Patent as granted. Basis for inflammation associated with joint pain, swelling or septic shock is in Claim 28 of the Patent as granted.

5.22 Amended Claim 31 has basis in Claim 1, part h), of the Patent as granted. Claim 31 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for systemic lupus erythematosis, myasthenia gravis, multiple sclerosis and rheumatoid arthritis is in Claim 18 of the Patent as granted. Basis for asthma, bronchitis, emphysema and end stage renal failure is in Claim 19 of the Patent as granted. Basis for renal neoplasms, multiple myelomas, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for inflammation associated with joint pain, swelling, anaemia or septic shock is in Claim 28 of the Patent as granted. Basis for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation is in Claims 22-25 of the Patent as granted.

5.23 Amended Claim 32 has basis in Claim 1, part l) of the Patent as granted. Claim 32 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for end stage renal failure is in Claim 19 of the Patent as granted. Basis for multiple myelomas and lymphomas is in Claim 21 of the Patent as granted. Basis for inhibiting antibody production associated with an autoimmune disease is in Claims 16-17 of the Patent as granted. Basis for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation is in Claims 22-25 of the Patent as granted.

5.24 Amended Claim 33 has basis in Claim 2 of the Patent as granted.

5.25 Amended Claim 34 has basis in Claim 3b) of the Patent as granted. Claim 34 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for treating asthma, bronchitis and emphysema is in Claim 19 of the Patent as granted. Basis for treating nephritis and pyelonephritis is in Claim 20 of the Patent as granted. Basis for treating renal neoplasms, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for treating Crohn's Disease is in Claim 26 of the Patent as granted. Basis for treating inflammation associated with joint pain, swelling or septic shock is in Claim 28 of the Patent as granted.

5.26 Amended Claim 35 has basis in Claim 3c) of the Patent as granted. Claim 35 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for systemic lupus erythematosis, myasthenia gravis, multiple sclerosis and rheumatoid arthritis is in Claim 18 of the Patent as granted. Basis for asthma, bronchitis, emphysema and end stage renal failure is in Claim 19 of the Patent as granted. Basis for renal neoplasms, multiple myelomas, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for inflammation associated with joint pain, swelling anaemia or septic shock is in Claim 28 of the Patent as granted. Basis for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation is in Claims 22-25 of the Patent as granted.

5.27 Amended Claim 36 has basis in Claim 3d) of the Patent as granted. Claim 36 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for treating asthma, bronchitis and emphysema is in Claim 19 of the Patent as granted. Basis for nephritis and pyelonephritis is in Claim 20 of the Patent as granted. Basis for renal neoplasms, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for Crohn's Disease is in Claim 26 of the Patent as granted. Basis for inflammation associated with joint pain, swelling or septic shock is in Claim 28 of the Patent as granted.

5.28 Amended Claim 37 has basis in Claim 3g) of the Patent as granted. Claim 37 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for treating asthma, bronchitis and emphysema is in Claim 19 of the Patent as granted. Basis for nephritis and pyelonephritis is in Claim 20 of the Patent as granted. Basis for renal neoplasms, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for Crohn's Disease is in Claim 26 of the Patent as granted. Basis for inflammation associated with joint pain, swelling or septic shock is in Claim 28 of the Patent as granted.

5.29 Amended Claim 38 has basis in Claim 3h) of the Patent as granted. Claim 38 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for systemic lupus erythematosis, myasthenia gravis, multiple sclerosis and rheumatoid arthritis is in Claim 18 of the Patent as granted. Basis for asthma, bronchitis, emphysema and end stage renal failure is in Claim 19 of the Patent as granted. Basis for renal neoplasms, multiple myelomas, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for inflammation associated with joint pain, swelling anaemia or septic shock is in Claim 28 of the Patent as granted. Basis for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation is in Claims 22-25 of the Patent as granted.

5.30 Amended Claim 39 has basis in Claim 3j) of the Patent as granted. Claim 39 has also been amended to recite medical conditions that are treatable using the claimed medicament. Basis for myasthenia gravis is in Claim 18 of the Patent as granted. Basis for bronchitis, emphysema and end stage renal failure is in Claim 19 of the Patent as granted. Basis for renal neoplasms, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for Crohn's Disease is in Claim 26 of the Patent as granted. Basis for inflammation associated with joint pain or swelling is in Claim 28 of the Patent as granted.

5.31 Amended Claim 40 has basis in Claim 3m) of the Patent as granted. Claim 40 has also been amended to recite medical conditions that are treatable using the claimed

medicament. Basis for asthma, bronchitis and emphysema is in Claim 19 of the Patent as granted. Basis for nephritis and pyelonephritis is in Claim 20 of the Patent as granted. Basis for renal neoplasms, light chain neuropathy and amyloidosis is in Claim 21 of the Patent as granted. Basis for Crohn's Disease is in Claim 26 of the Patent as granted. Basis for inflammation associated with joint pain, swelling or septic shock swelling is in Claim 28 of the Patent as granted.

5.32 Amended Claim 41 has basis in Claim 4 of the Patent as granted. In more detail, parts a)-c) of amended Claim 48 correspond to parts c)-e) of Claim 4 as granted.

5.33 Amended Claim 42 also has basis in Claim 4 of the Patent as granted. In more detail, parts a)-d) of amended Claim 49 correspond to parts a) and f)-h) of Claim 4 as granted.

5.34 Amended Claims 43-45 have basis in Claim 5 and Claim 6, parts b) and c) respectively, of the Patent as granted.

5.35 Amended Claims 46 and 47 have basis in Claim 7, parts b) and c) respectively, of the Patent as granted.

5.36 Amended Claims 48-52 correspond to Claims 8-12 of the Patent as granted.

5.37 Amended Claim 53 has basis in Claim 18 of the Patent as granted.

5.38 Amended Claim 54 has basis in Claim 26 of the Patent as granted.

5.39 Amended Claim 55 has basis in Claim 20 of the Patent as granted.

Conclusion on basis for amended Claims 1-55 (Auxiliary Request 1)

5.40 The amended claims do not introduce subject-matter that extends beyond the content of the application as filed, in accordance with Article 123(2) EPC; and the amended claims do not extend the protection conferred, in accordance with Article 123(3) EPC.

6 NOVELTY – Article 54 EPC, Article 100a EPC

Article 54 EPC

6.1 According to Article 54(1) EPC, an invention shall be considered to be new if it does not form part of the state of the art. The state of the art is defined in Articles 54(2) and 54(3) EPC.

Novelty

6.2 The compounds *per se* recited in Claim 1 of Auxiliary Request 1 are novel with regard to the cited prior art, which fails to disclose BR43x2, antibodies that bind specifically thereto, antibodies that bind specifically to SEQ ID NO: 10, or the specific fragments of SEQ ID NO: 8. Hence, the use of these compounds as recited in amended Claim 1 is also novel with respect to the cited prior art.

Furthermore, the prior art fails to disclose the mechanism of action of the novel polypeptides and antibodies recited in Claim 1. In more detail, there is no disclosure in any of the cited prior art that the presently claimed compounds can be used to inhibit ztnf4 activity.

In addition, the prior art fails to disclose using the novel compounds of Claim 1 for the manufacture of a medicament for treating a medical condition by inhibiting ztnf4 activity. In particular, there is no disclosure in the prior art of using the claimed compounds to treat the specific conditions recited in Claim 1 by inhibiting ztnf4 activity.

Thus, Claim 1 is novel.

6.3 The compounds *per se* recited in Claim 3 of Auxiliary Request 1 are novel with regard to the prior art. Hence, the use of these compounds as recited in amended Claim 3 is also novel with respect to the cited prior art.

In addition, there is no disclosure in the prior art of the recited mechanism of action of

the novel polypeptides and antibodies recited in Claim 3. In more detail, the relevant prior art fails to disclose inhibition of BR43x2, TACI or BCMA receptor-ztnf4 engagement by the presently claimed compounds.

Furthermore, there is no disclosure in the prior art of using the claimed compounds for the manufacture of a medicament for treating a medical condition by inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement. In particular, there is no disclosure in the prior art of using the claimed compounds to treat the specific medical conditions recited in Claim 3 by inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement.

Thus, Claim 3 is novel.

6.4 Dependent "use" Claims 2 and 4-16 of Auxiliary Request 1 are novel by virtue of their dependency on novel independent Claims 1 and 3.

6.5 Claims 17-23 of Auxiliary Request 1 (7 January 1999) relate to BR43x2 aspects of the present invention – namely, novel SEQ ID NOs: 1 and 2, which are disclosed for the first time in the present application. There is no disclosure in any of the cited prior art of the isolated polynucleotide molecule of Claims 17 or 18, or the isolated polypeptide molecule of Claim 22, and hence Claims 17-23 of Auxiliary Request 1 are novel.

6.6 Claim 24 of Auxiliary Request 1 (7 January 1999). With particular regard to parts a) and b) of Claim 24, polypeptides of SEQ ID NOs: 2 or 4 were not known prior to the present invention, and hence antibodies that specifically bind to one of these sequences were also not known prior to the present invention. Antibodies that bind specifically to a polypeptide having the sequence of SEQ ID NO: 10 (a sequence based on the cysteine rich domain of the novel polypeptide BR43x2) are also novel over the cited prior art. In this regard, we refer to the definition of "specifically binding" in paragraph 0073 of the Patent as granted, and confirm that a person skilled in the art would consider it routine to identify the binding affinity (K_a) of a receptor, for example, by Scatchard analysis. Hence, Claim 24 of Auxiliary Request 1 is novel.

6.7 Dependent "composition" Claims 25 and 26 of Auxiliary Request 1 are novel by virtue

of their dependency on novel independent Claim 24.

6.8 With regard to Claim 27 of Auxiliary Request 1, none of the cited prior art documents discloses using a soluble polypeptide comprising the extracellular domain of TACI for the manufacture of a medicament for treating any of the recited specific medical conditions. Thus, Claim 27 is novel with respect to the cited prior art.

6.9 Claim 28 of Auxiliary Request 1 is also novel over all the cited prior art, which fails to disclose the use of a polypeptide comprising the extracellular domain of BCMA for the manufacture of a medicament for treating any of the recited specific medical conditions. Thus, Claim 28 is novel with respect to the cited prior art.

6.10 None of the cited prior art discloses the use of a polypeptide comprising the sequence of SEQ ID NO: 10 for the manufacture of a medicament for treating the specific medical conditions recited in Claim 29 of Auxiliary Request 1. Thus, Claim 29 is novel.

6.11 Claim 30 of Auxiliary Request 1 is novel, since none of the cited prior art documents discloses using an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 6 for manufacture of a medicament for treating any of the specific medical conditions recited in Claim 30. Thus, Claim 30 is novel.

6.12 Claim 31 of Auxiliary Request 1 is also novel over the cited prior art. The cited documents fail to disclose using an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 8 for manufacture of a medicament for treating the specific medical conditions of Claim 31. Thus, Claim 31 is novel over the cited prior art.

6.13 Claim 32 of Auxiliary Request 1 (7 January 1999) is novel over the cited prior art. In more detail, the recited mechanism of action of amino acid residues 1-166 of SEQ ID NO: 6 was not known prior to 7 January 1999.

In this regard, neither of the pre-7 January 1999 prior art citations that describe TACI (Master references D1 and D9) discloses <u>any</u> specific ligand for TACI, let alone ztnf4.

Thus, D1 and D9 do not make a connection between any therapy and any specific ligand, let alone ztnf4. Specifically, none of the pre-7 January 1999 citations discloses using amino acid residues 1-166 of SEQ ID NO: 6 to inhibit ztnf4 activity. Thus, said prior art is not novelty-destroying in the context of ztnf4 activity.

TACI is a member of the TNF family of receptors. TNF receptors demonstrate a broad range of binding abilities, and are known to bind a large number of different ligands (see enclosed Master reference D32, in particular Figure 1). In this regard, a single TNF receptor may bind more than one different ligand, which binding would be expected to lead to the activation of different downstream pathways. By way of example, TACI is known to bind APRIL and BAFF (also known as ztnf4, neutrokine α, Blys, TALL-1 and THANK, see paragraph 0003 of the Patent as granted), and additional TACI ligands are anticipated. In this regard, a large number of "orphan" ligands have been identified, and some of these may be ligands for TACI. Thus, ztnf4 should be regarded as a specific selection from the possible ligands that act through TACI, said selection making available to the public (for the first time) a unique binding interaction.

Hence, inhibition of ztnf4 activity is a specific selection from all the possible activities of amino acid residues 1-166 of SEQ ID NO: 6, and inhibiting ztnf4 is distinct from inhibiting other TACI ligands (or from inhibiting TACI). Thus, the prior art, which discusses inhibition of TACI in generic terms, does not destroy the novelty of inhibiting activity of the species ztnf4.

Furthermore, there is no disclosure in the prior art of applying the ztnf4-inhibiting properties of amino acid residues 1-166 of SEQ ID NO: 6 for treating a medical condition. In particular, there is no disclosure in the prior art of using amino acid residues 1-166 of SEQ ID NO: 6 to treat the specific conditions recited in Claim 32 by inhibiting ztnf4 activity. Thus, Claim 32 is novel over the cited prior art.

6.14 Claim 33 of Auxiliary Request 1 is novel by virtue of its dependency on any of novel Claims 27-32.

6.15 With regard to Claim 34 of Auxiliary Request 1, none of the cited prior art documents

disclose using a soluble polypeptide comprising the extracellular domain of TACI for the manufacture of a medicament for treating any of the recited specific medical conditions. Thus, Claim 34 is novel with respect to the cited prior art.

6.16 Claim 35 of Auxiliary Request 1 is also novel over all the cited prior art, which fails to disclose the use of a polypeptide comprising the extracellular domain of BCMA for the manufacture of a medicament for treating any of the recited specific medical conditions. Thus, Claim 35 is novel with respect to the cited prior art.

6.17 None of the cited prior art discloses the use of a polypeptide comprising the sequence of SEQ ID NO: 10 for the manufacture of a medicament for treating the specific medical conditions recited in Claim 36 of Auxiliary Request 1. Thus, Claim 36 is novel.

6.18 Claim 37 of Auxiliary Request 1 is novel, since none of the cited prior art documents discloses using an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 6 for manufacture of a medicament for treating any of the specific medical conditions recited in Claim 37. Thus, Claim 37 is novel.

6.19 Claim 38 of Auxiliary Request 1 is also novel over the cited prior art. The cited documents fail to disclose using an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 8 for manufacture of a medicament for treating the specific medical conditions of Claim 38. Thus, Claim 38 is novel.

6.20 With regard to Claim 39 of Auxiliary Request 1, none of the cited prior art discloses using an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 18 for manufacture of a medicament for treating the specific medical conditions recited in Claim 39. Thus, Claim 39 is novel over the cited prior art.

6.21 None of the cited documents discloses the use of amino acid residues 1-166 of SEQ ID NO: 6 for manufacture of a medicament for treating the specific medical conditions recited in Claim 40 of Auxiliary Request 1. Thus, Claim 40 is novel.

6.22 Claims 41-55 of Auxiliary Request 1 are novel by virtue of their dependency.

Conclusion on Novelty

6.23 All the claims of Auxiliary Request 1 are novel with regard to the prior art cited by Opponents I-IV.

7 INVENTIVE STEP - Article 56 EPC, Article 100a EPC

Article 56 EPC

7.1 According to Article 56 EPC, an invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art.

Inventive Step

7.2 The novel claims of Auxiliary Request 1 are inventive in view of all the cited prior art, since none of these cited documents provides any suggestion of the claimed uses, products or compositions.

Inventive Step of Claims 1 and 3

BR43x2 aspects

7.3 There is no suggestion in the prior art of any of the BR43x2 aspects of the presently claimed invention (parts a-c) and e) of Claim 1, and parts a-c) and h) of Claim 3 of Auxiliary Request 1). In particular, Master reference D1 (on page 19, line 20) indicated that there are no reported DNA sequences that are closely related to that for TACI. Thus, BR43x2, which is a TACI isoform, would not have been obvious in view of D1.

7.4 In this regard, the receptor BR43x2 was identified as a result of detailed and lengthy studies carried out by the inventors of the Patent, using their expert skills and knowledge. Prior to the identification of the BR43x2 polypeptide, in its full-length and soluble forms, it would not have been possible (and in any case there would have been no motivation) to identify antibodies or antibody fragments that bind specifically to SEQ ID NO: 2 or 4. Furthermore, the inventive provision of the BR43x2 sequences and antibodies has also enabled the identification of the claimed inventive therapeutic uses thereof. None of this would have been possible prior to the present invention, and hence all uses of BR43x2 polypeptides and antibodies are inventive over the

cited prior art.

7.5 Moreover, there was a clear prejudice in the art (prior to the present invention), which teaches away from use of a TNF receptor having only a single "cysteine-rich domain" (CRD). In this regard, it is clear from paragraphs 0017-0019 of the Patent that members of the TNF family of receptors typically contain several conserved cysteine-rich domains (commonly 4 repeating domains). TACI contains 2 cysteine-rich domains, the first of which is highly conserved, and the second of which is poorly conserved. Thus, a skilled person seeking to identify further TACI-like TNF receptor family members would look for sequences containing at least 2 cysteine-rich domains. In particular, when looking for a new isoform of TACI, the skilled person would expect the isoform to comprise at least the first, highly conserved cysteine-rich domain.

7.6 In contrast, the BR43x2 polypeptide surprisingly contains only one cysteine-rich domain. Even more surprisingly, this single cysteine-rich domain does not correspond to the first, highly conserved TACI cysteine-rich domain but to the second, poorly conserved cysteine-rich domain. This is exactly the opposite of what a skilled person would have expected, based on the teachings of the prior art.

7.7 Given the fact that the BR43x2 polypeptide has only one cysteine-rich domain - and particularly given the fact that this repeat is poorly conserved with respect to the TNF receptor family - a skilled person would expect that BR43x2 polypeptides would not bind a TNF ligand such as ztnf4, and that said polypeptides would therefore lack therapeutic activity. In particular, a skilled person at the filing date of the Patent would not have expected the BR43x2 polypeptides recited in Claims 1 and 3 of Auxiliary Request 1 to bind and inhibit ztnf4 activity, as presently claimed.

7.8 Example 1 of the Patent as granted describes the identification of the BR43x2 polypeptide using a secretion trap screen, and confirms that the BR43x2 polypeptide binds to ztnf4 with high affinity using its single cysteine-rich domain. This would not have been obvious to a skilled person at the filing date of the Patent, to whom the prior art suggested that at least the first, conserved, cysteine-rich domain was necessary for receptor function (preferably at least 2 cysteine-rich domains).

Example 3 of the patent as granted also confirms that ztnf4 is a ligand for the BR43x2 polypeptide and acts to stimulate B-cell proliferation via BR43x2 *in vitro* (see Tables 5 and 6 on page 21 of the Patent specification). As recited in paragraph 0112 of the Patent as granted, the results indicate that soluble ztnf4 (acting via the BR43x2 polypeptide) promotes B cell proliferation and Ig production.

Hymowitz *et al.* (newly cited Master reference D33) also confirms that the receptor BR43x2 engages BAFF (=ztnf4) with unexpectedly high affinity.

7.9 Hence, all BR43x2 aspects of Auxiliary Request 1 and, in particular, parts a-c) and e) of Claim 1, and parts a-c) and h) of Claim 3, are inventive with respect to the cited prior art.

Antibodies that specifically bind to a polypeptide of SEQ ID NO: 10

7.10 The antibodies recited in Claims 1d) and 3d) of Auxiliary Request 1, which bind specifically to a polypeptide of SEQ ID NO: 10, are not suggested by any of the cited prior art. In this regard, as illustrated in paragraph 0019 of the Patent as granted, SEQ ID NO: 10 represents an amino acid sequence based on the single cysteine-rich domain (CRD) of the novel polypeptide BR43x2.

The cited prior art allegedly describes antibodies that bind to the TACI polypeptide and antibodies that bind to the BCMA polypeptide, as well as to soluble fragments of these polypeptides. However, there is no suggestion in the cited prior art of any antibody that specifically binds to a polypeptide represented by the sequence SEQ ID NO: 10, which sequence is based on the single CRD of the novel polypeptide BR43x2.

7.11 The CRD of the BR43x2 polypeptide is poorly conserved. As illustrated in Figure 1 of the Patent, the CRD of BR43x2 differs from the first CRD of TACI (only 46% identity) and the CRD of BCMA (only 35% identity). The only sequence that corresponds to the CRD of BR43x2 is the second CRD of TACI - which sequence is missing from the BCMA polypeptide.

In this regard, the TACI CRD is located in the middle of the TACI extracellular domain, and is thus in a different antigenic environment to the BR43x2 CRD, which is N-terminal. Thus, antibodies raised against the TACI CRD would not specifically bind to the BR43x2 CRD, and hence would not bind specifically to a polypeptide of SEQ ID NO: 10.

7.12 Furthermore, the "Prosite" consensus sequence, provided on page 19, lines 20-25, of Master reference D1 does not disclose the sequence of SEQ ID NO: 10. In this regard, the "Prosite" sequence is more flexible than (ie. broader than) SEQ ID NO: 10 – ie. the sequence of SEQ ID NO: 10 is more specific than the D1 "Prosite" consensus sequence. In particular, the D1 Prosite sequence differs widely from the sequence of SEQ ID NO: 10 between the 5th and 6th Cys residues. We refer in this regard to the sequence comparison illustrated in Master reference D34.

7.13 Thus, even the D1 anti-"Prosite" antibodies would not bind specifically to a polypeptide having the sequence of SEQ ID NO: 10, which is relatively more specific than the D1 "Prosite" sequence. Hence, the use of the recited specifically binding antibodies, which bind to a polypeptide having the more specific sequence of SEQ ID NO: 10, would not have been obvious to a skilled person, and Claims 1d) and 3d) of Auxiliary Request 1 are inventive.

7.14 With regard to the citable "BCMA" prior art (Master references D10-D13), as mentioned above, the BCMA polypeptide has only a single CRD (corresponding to the first TACI CRD) and BCMA lacks any sequence corresponding to the BR43x2 CRD. Furthermore, the only prior art document to describe the BCMA CRD (Master reference D12) fails to suggest any antibodies to this particular sequence. Thus, there is no suggestion in any of the BCMA prior art of an antibody that specifically binds to a polypeptide of SEQ ID NO: 10.

7.15 In this regard, the only antibodies described in the BCMA prior art (detailed in Master reference D13, "Preparation of polyclonal anti-BCMA antisera", page 1094) were raised against a BCMA-GST fusion protein, in which the BCMA portion lacked the N-terminal 12 amino acids. There is no suggestion of raising antibodies against a BCMA molecule having an intact N-terminus. Since the BCMA CRD is found in amino

acids 8-41 of SEQ ID NO: 8, the first 5 amino acids of this sequence were absent from the D13 antigen. Thus, it is clear that the BCMA prior art provides no suggestion of antibodies that bind specifically to a cysteine rich domain sequence. Thus, antibodies that specifically bind to a polypeptide of SEQ ID NO: 10 would not have been obvious to a skilled person from D10-D13.

7.16 In addition, none of the cited prior art provides any suggestion of the presently claimed uses of an antibody/ fragment that specifically binds to a polypeptide of SEQ ID NO: 10. In particular, it would not have been obvious to a skilled person reading the cited prior art that these antibodies should (or even could) be used in a medicament for inhibiting ztnf4 activity or for inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagements. Furthermore, there is no suggestion in the prior art to use an antibody that specifically binds to a polypeptide of SEQ ID NO: 10 for the manufacture of a medicament for treating any medical condition, let alone the specific conditions recited in Claims 1 and 3 of Auxiliary Request 1. Thus, Claims 1d) and 3d) of Auxiliary Request 1 are inventive in view of the cited prior art.

Amino acid residues 8-37, 1-48, 1-37 and 8-48 of SEQ ID NO: 8

7.17 There is no suggestion in any of the cited prior art (in particular, in none of the cited "BCMA" prior art) of any of these specific amino acid sequence fragments. Thus, parts f) – i) of Claim 1, and parts i) - l) of Claim 3 of Auxiliary Request 1 have an inventive step with regard to the cited prior art.

7.18 In more detail, it would not have been obvious from the cited prior art that these short fragments would have the required biological activity – namely, use for treating the recited specific medical conditions by inhibiting ztnf4 activity or by inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagements. Indeed, a skilled person would expect these fragments to have no useful function at all.

7.19 In this regard, none of the Master reference "BCMA" citations D10-D11 or D13 refers to the N-terminal region of the SEQ ID NO: 8 polypeptide, from which the recited fragments are obtained. In particular, no special technical function is ascribed to this region. D12 allegedly describes a cysteine rich domain within this region, but does

suggest the specific sequence fragments amino acids 8-37, 1-48, 1-37 or 8-48 of SEQ ID NO: 8. In particular, D12 does not suggest that this region would be useful for treating any medical condition by inhibiting ztnf4 activity or by inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagements.

7.20 In contrast, the inventors of the Patent have identified specific fragments of BCMA that are useful for inhibiting ztnf4 activity and/ or for inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagements. In more detail, by identification of the cysteine-rich domain (CRD) of novel polypeptide BR43x2, and hence the sequence of SEQ ID NO: 10, the present inventors have thereby identified that amino acids 1-48 and 8-48 of SEQ ID NO: 8 embrace the CRD of BCMA. Surprisingly, the present inventors have identified that these small fragments of BCMA are sufficient for obtaining the desired biological activity, in the absence of other regions of the BCMA polypeptide. Furthermore, identification of the BR43x2 CRD (and hence SEQ ID NO: 10) has also enabled the present inventors to identify fragments of amino acid sequence 1-37 of SEQ ID NO: 8, and in particular, amino acids 8-37 of SEQ ID NO: 8, which represents a fragment of the BCMA CRD. Surprisingly, despite the fact that the complete CRD is not present, these fragments also have the desired biological activity.

7.21 Hence, the specific fragments of SEQ ID NO: 8 (amino acids 8-37, 1-48, 1-37 and 8-48) – and thus SEQ ID NO: 10 - would not have been obvious to a skilled person reading D11-D13. In particular, a skilled person would not have considered it obvious that these short fragments (or SEQ ID NO: 10) have the desired biological activity of inhibiting ztnf4 activity and/ or inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagements. Furthermore, it would not have been obvious to a skilled person to use these specific fragments (or SEQ ID NO: 10) for the manufacture of a medicament for treating any medical conditions, let alone the specific medical conditions recited in Claims 1 and 3 of Auxiliary Request 1.

7.22 The findings of the Proprietor have been confirmed by Master reference D3 (not citable for inventive step against Auxiliary Request 1), which shows that the cysteine rich domain of BCMA is located at residues 8-41 of SEQ ID NO: 8. Furthermore, as illustrated in the very recent paper Master reference D33, the specific sequence fragments recited in Claims 1 and 3 of Auxiliary Request 1 (and thus SEQ ID NO: 10)

are important for binding of BCMA to ztnf4 (BAFF).

7.23 The biological function of these fragments is further supported by Master references D38 and D39, which describe binding experiments carried out using a fusion protein containing residues 1-48 of SEQ ID NO: 8 (BCMA-Ig). As reported in the passage spanning pages 997-998 of D38 (and Figure 3c), the BCMA-Ig fusion protein prevented ztnf4 from binding to human B cells and completely inhibited ztnf4 stimulatory activity on B cells. D39 (right-hand column on page 131-page 132 and Figure 1) also reports that the BCMA-Ig fusion protein binds BAFF (=ztnf4) and blocks binding of BAFF to Raji cells. Furthermore (pages 133-134), D39 reports that in vivo treatment with the BCMA-Ig reduced the B cell population in normal mice by 50% compared to the control – thus confirming that residues 1-48 of SEQ ID NO: 8 are useful for treating B cell mediated autoimmune diseases and B cell cancers. Thus, D38 and D39 confirm that residues 1-48 of SEQ ID NO: 8 are sufficient for high-affinity binding to ztnf4, and are therapeutically useful.

7.24 Hence, Claim 1f+g) and Claim 3i+j) of Auxiliary Request 1 have an inventive step over the cited prior art.

Antibodies that specifically bind to a polypeptide of SEQ ID NO: 59, 60 or 20

7.25 There is absolutely no suggestion of these antibodies in any of the cited prior art documents – and in particular, there is no suggestion of using these antibodies as recited in Claim 3. Thus, Claim 3 parts e-g) is inventive over the cited prior art.

7.26 The specific polypeptides against which these antibodies have been raised are not suggested in the prior art, and in particular there is no suggestion of using these fragments as antigens. Thus, a skilled person would not consider it obvious to raise an antibody against these sequences.

7.27 In particular, with regard to Claim 3g), we would mention that the sequence of murine TACI (SEQ ID NO: 20) differs considerably from that of human TACI (SEQ ID NO: 6) and thus would not be obvious from the cited "TACI" prior art - Master references D1 and D9 – which provide the human sequence only. We refer in this regard to Master

reference D37, Figure 1, which compares the human and murine TACI sequences and determines that they are only 54% identical. Thus, the use of an antibody that specifically binds to a polypeptide of SEQ ID NO: 20 would not be obvious in the light of the cited prior art.

7.28 In contrast, the present inventors have prepared these antibodies and have demonstrated their utility. In more detail, Example 18 illustrates binding of anti-SEQ ID NO: 59 and anti-SEQ ID NO: 60 antibodies to their target ztnf4 sequences, thereby inhibiting ztnf4 activity and/ or inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagements. This would not have been obvious to a skilled person, and hence Claim 3 e-g) is inventive.

7.29 In summary, independent Claims 1 and 3 of Auxiliary Request 1 are inventive over the cited prior art, which fails to suggest either the specific compounds recited, or the specific uses to which they are put - namely use for the manufacture of a medicament for treating a range of specific medical conditions by inhibiting ztnf4 activity and/ or inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagements.

Dependent Claims 2 and 4-16

7.30 Claim 2 of Auxiliary Request 1 depends on Claim 1, which is inventive over all the cited prior art, as discussed above. Claims 4-16 of Auxiliary Request 1 all depend on either Claim 1 or Claim 3, which are both inventive over all the cited prior art, as discussed above. Thus, Claims 2 and 4-16 are all inventive by virtue of their dependency.

Claims 17-23

7.31 Claims 17-23 of Auxiliary Request 1 all relate to BR43x2 aspects of the present invention, which, as discussed above (paragraphs 7.3 – 7.9) are inventive over the cited prior art. In more detail, there is no suggestion in any of the cited prior art documents of the polynucleotide of Claim 17 or 18, or of the polypeptide of Claim 22, and a skilled person would not have considered these sequences to be obvious. In particular, in view of the above-described prejudice in the art away from TNF-family

receptors that have only one cysteine rich pseudo repeat, and more specifically, away from a TACI isoform that lacks the first, highly conserved repeat, a skilled person would have been led away from the presently claimed sequences.

7.32 Thus, BR43x2 SEQ ID NOs: 1 and 2 are inventive over prior art TNF-family receptor sequences, and Claims 17-23 of Auxiliary Request 1 have an inventive step.

Claims 24-26

7.33 Claims 24-26 are inventive over the cited prior art for the same reasons as discussed above with regard to Claims 1 and 3. In this regard, the antibodies recited in parts a-c) of Claim 24 are the same as those recited in parts b-d) of Claims 1 and 3.

7.34 Furthermore, since the antibodies themselves would not have been obvious to a skilled person, and it would not have been obvious that they would be therapeutically useful, it would also not have been obvious to make a pharmaceutical composition comprising these antibodies. Thus, pharmaceutical compositions of inventive antibodies, as claimed in Claims 24-26 of Auxiliary Request 1, are inventive with respect to the cited prior art.

Claims 27, 30, 34, 37 and 40

7.35 Claims 27 and 34 of Auxiliary Request 1 are a pair of corresponding claims, which differ from each other only in terms of their precise mechanism of action (last clause). Claims 30 and 37 of Auxiliary Request 1 are another pair of corresponding claims, which differ from each other only in terms of their precise mechanism of action (last clause). The two pairs of claims concern TACI aspects of the invention, namely a soluble polypeptide comprising the extracellular domain of TACI, and an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 6. The compound recited in Claim 40 is a more specific version of the compound of Claims 27 and 34. The same medical conditions are recited in all of these claims. Thus, Claims 27, 30, 34, 37 and 40 of Auxiliary Request 1 are considered together for the purposes of inventive step.

7.36 Claims 27, 30, 34, 37 and 40 are inventive since it would not have been obvious in view of any of the cited prior art to use the recited compounds for the manufacture of a medicament for treating the specific medical conditions recited in these claims.

7.37 With particular regard to the "TACI" prior art documents that have been cited for inventive step of these claims (Master references D1 and D9), no medical conditions whatsoever are described in D9, which is a merely academic publication. Turning to D1, this document provides no suggestion of treating any airway disorders – and hence treatment of asthma, bronchitis and emphysema is inventive. Furthermore, there is no suggestion of treating the specific renal diseases nephritis and pyelonephritis, or of treating renal neoplasms, light chain neuropathy or amyloidosis. "Autoimmune diseases" are numerous and very varied, each requiring specialist treatment. Hence, alleged general disclosures in the prior art of treating autoimmune diseases would not lead a skilled person to consider treatment of the specific condition Crohn's disease. Similarly, there are many different types of inflammation, and general references to treating "inflammation" would not lead a skilled person to consider treating inflammation associated with joint pain, swelling or septic shock.

7.38 Also with particular regard to Master references D1 and D9, there is no suggestion in these documents of any particular ligand for TACI, let alone the ztnf4 ligand. Thus, it would not have been obvious to a skilled person reading D1 or D9 that a soluble polypeptide comprising the extracellular domain of TACI, or an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 6, should (or even could) be used to inhibit ztnf4 activity or to inhibit BR43x2, TACI or BCMA receptor-ztnf4 engagements, as claimed in Claims 27, 30, 34 or 37 and 40. Likewise, it would not have been obvious that amino acids 1-166 of SEQ ID NO: 6 could be used to inhibit BR43x2, TACI or BCMA receptor-ztnf4 engagements, as claimed in Claim 40 of Auxiliary Request 1.

7.39 Furthermore, with particular regard to Claims 30 and 37 of Auxiliary Request 1, Example 18 of the Patent demonstrates the unexpectedly good results achieved using antibodies that specifically bind to a polypeptide of SEQ ID NO: 6. In more detail, monoclonal anti-TACI antibodies 248.23 and 246.3 reduce binding of ztnf4 to TACI by 50% in diluted conditioned media, and by 2-fold and 5-fold, respectively, in undiluted

media. Thus, the recited anti-TACI antibodies of Claims 30 and 37 of Auxiliary Request 1 are useful for inhibiting ztnf4 activity and inhibiting receptor-ztnf4 engagements. These results have been confirmed by the Proprietor's own unpublished data (Master reference D36), which illustrate that the anti-TACI monoclonal antibody 248.23 blocks binding of biotin-labelled ztnf4 to TACI-BHK cells by a level of 4-fold over background. This document also confirms that the 3 anti-TACI antibodies described in Example 18 of the Patent are specific for the SEQ ID NO: 6 polypeptide since they do not demonstrate any binding to BCMA-transfected BHK cells.

7.40 Thus, Claims 27, 30, 34, 37 and 40 of Auxiliary Request 1 are all inventive over the cited prior art.

Claims 28, 31, 35 and 38

7.41 Claims 28 and 35 are a pair of corresponding claims, which differ from each other only in terms of their precise mechanism of action (last clause). Claims 31 and 38 are another pair of corresponding claims, which differ from each other only in terms of their precise mechanism of action (last clause). All these claims relate to BCMA aspects and recite the same medical conditions. Hence, these claims are considered together for the purposes of inventive step.

7.42 Claims 28, 31, 35 and 38 of Auxiliary Request 1 have an inventive step over the relevant cited prior art (Master references D10-D13), which fails to suggest any therapeutic use of the recited compounds, let alone using these specific compounds for treating the particular medical conditions recited in these claims.

7.43 In more detail, D10-D13 are all merely academic papers, which are not concerned with medical uses of BCMA or of antibodies thereto. Thus, it would not have been obvious to a skilled person reading any of D10-D13 that a polypeptide of SEQ ID NO: 8, or an antibody/ antibody fragment that specifically binds to said polypeptide, should (or even could) be used to treat systemic lupus erythematosis, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, asthma, bronchitis, emphysema, end stage renal failure, renal neoplasms, multiple myelomas, light chain neuropathy, amyloidosis

or inflammation associated with joint pain, swelling, anaemia or septic shock; or for inhibiting effector T cells wherein said inhibition comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation, as presently claimed.

7.44 In this regard, vague references in D10-D13 to localization of BCMA in B cell lines, and to possible roles in the immune system would not lead a skilled person to consider using a polypeptide comprising the extracellular domain of BCMA, or an antibody thereto, for treating an autoimmune disease. In particular, it would not be obvious that the recited compounds should (or even could) be used to treat the specific conditions recited in Claims 28, 31, 35 and 38.

7.45 Furthermore, with regard to Claims 31 and 38 of Auxiliary Request 1, the antibodies described in D10-D11 and D13 (in particular D13) were raised against a BCMA-GST fusion, which lacked the N-terminal 12 amino acid residues. There is no suggestion of raising an anti-BCMA antibody against a polypeptide of SEQ ID NO: 8, as presently claimed. In more detail, the prior art BCMA antigen is N-terminally truncated and thus lacks a portion of the important cysteine-rich domain. Said prior art antigen is therefore likely to have a different antigenic configuration compared to a polypeptide of SEQ ID NO: 8. Thus, a skilled person following the teaching of D13 would produce an "anti-BCMA" antibody that would not bind specifically to a polypeptide of SEQ ID NO: 8, as required by Claims 31 and 38 of Auxiliary Request 1. D13 teaches a skilled person away from antibodies that bind specifically to a polypeptide of SEQ ID NO: 8, and hence Claims 31 and 38 of Auxiliary Request 1 have an inventive step.

Claims 29 and 36

7.46 Claims 29 and 36 of Auxiliary Request 1 differ only in terms of the specific mechanism of action recited in the last clause, and hence they are considered together with respect to inventive step.

7.47 Claims 29 and 36 are inventive over the citable prior art documents, which fail to suggest using a polypeptide comprising the sequence of SEQ ID NO: 10 for treating the specific medical conditions recited in Claims 29 and 36. In this regard, D9 and

D10-D13 are of a merely academic nature and do not describe any therapeutic applications. With regard to D1, the generally described therapeutic applications provide no suggestion (to a skilled person) to treat the specific medical conditions recited in Claims 29 and 36, which require particular therapeutic considerations. Thus, Claims 29 and 36 have an inventive step.

Claim 39

7.48 Numerous "ztnf4" prior art documents have been cited by the opponents, yet only Master reference D5 describes the specific polypeptide sequence SEQ ID NO: 18. However, this document fails to provide any suggestion of using antibodies that bind specifically to a polypeptide of SEQ ID NO: 18 to treat the specific medical conditions recited in Claim 39. Thus, Claim 39 is inventive over the cited prior art.

7.49 In this regard, there is no suggestion in D5 that the antibodies of Claim 39 should (or even could) be used to treat end stage renal failure, or to treat light chain neuropathy or amyloidosis. In view of alleged general references in D5 to treating autoimmune diseases, a skilled person would not consider obvious the treatment of the specific and distinct autoimmune diseases myasthenia gravis and Crohn's Disease. Furthermore, treating asthma is not equivalent to and would not render obvious any therapy for treating the distinct medical conditions of bronchitis and emphysema. In addition, alleged references to generic "tumours" and "inflammatory diseases" would not lead a skilled person to consider treating the specific conditions of renal neoplasms and inflammation associated with joint pain or swelling.

Claim 32

7.50 Claim 32 of Auxiliary Request 1 is inventive over the citable (pre- 7January 1999) prior art, since none of these documents provides any suggestion of the specific mechanism of action of amino acids 1-166 of SEQ ID NO: 6, recited in Claim 32. In particular, the subject-matter of Claim 32 is not suggested by the citable "TACI" prior art (Master references D1 and D9).

7.51 As discussed above, neither of Master references D1 and D9 describes any ligand for

the TACI receptor, let alone the specific ligand ztnf4. Thus, in view of D1 or D9, a skilled person would not consider it obvious to use amino acid residues 1-166 of SEQ ID NO: 6 to inhibit ztnf4 activity.

7.52 In contrast, the present inventors have identified that amino acids 1-166 of TACI can be used, surprisingly, to inhibit the activity of ztnf4. In particular, the present inventors have identified that this extracellular TACI sequence is unexpectedly useful for manufacture of a medicament for treating a range of specific medical conditions, as recited in Claim 32 of Auxiliary Request 1.

7.53 As previously discussed, TACI binds multiple ligands (see D32), one of which is ztnf4. Thus, identification of ztnf4 represents an inventive selection from the possible ligands that act through TACI, and inhibition of ztnf4 activity, is a specific and inventive selection from all the possible activities of amino acid residues 1-166 of SEQ ID NO: 6. In particular, inhibiting ztnf4 is distinct from inhibiting any TACI ligand (and from inhibiting TACI). Thus, the prior art, which discusses inhibition of TACI in general terms, would not provide any suggestion to a skilled person of inhibiting the activity of ztnf4. Thus, Claim 32 is inventive over the cited prior art.

7.54 Furthermore, there is no disclosure in any of the cited prior art of using amino acid residues 1-166 of SEQ ID NO: 6 to treat a medical condition by inhibiting ztnf4 activity. In particular, there is no disclosure in the prior art of using amino acid residues 1-166 of SEQ ID NO: 6 to treat the specific conditions recited in Claim 32 by inhibiting ztnf4 activity. Thus, Claim 32 has an inventive step over the cited prior art.

Dependent Claims 33 and 41-55

7.55 Dependent Claims 33 and 41-55 of Auxiliary Request 1 are inventive over the cited prior art by virtue of their dependency.

Conclusion with regard to Inventive Step

7.56 None of the claimed subject-matter of Auxiliary Request 1 would have been obvious to a skilled person in view of the cited prior art, and hence Claims 1-55 of Auxiliary

Request 1 have an inventive step.

8 OBSERVATIONS IN REPLY TO OPPONENT I

ADDED MATTER – ARTICLE 123(2) EPC AND ARTICLE 100c EPC

Claim 3 as granted

8.1 In points 6-11 of the Statement of Grounds, Opponent I has alleged that Claim 3 of the Patent as granted - which recites "inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement" - unallowably adds subject-matter that extends beyond the content of the PCT application as filed. In this regard, the original wording of this clause was "...receptor-ligand engagement". This final clause is now to be found in Claims 3 and 34-40 of Auxiliary Request 1.

8.2 The Patent specification clearly focuses on inhibiting receptor-ztnf4 engagements (rather than engagements with any other ligand). Indeed, no other ligand for TACI or BCMA is discussed in the Patent. Consistent with this, all of the published PCT Claims 1-28 related to ztnf4.

Reference to ztnf4 is found throughout the PCT specification – see for example page 53, lines 4-16 (in particular, lines 4-5), which discloses binding of ztnf4 to BR43x2, TACI and BCMA. Furthermore, lines 18-20 on page 54 of the PCT specification recites an effect on cellular response to ztnf4 in the presence of soluble BR43x2, TACI and BCMA. In addition, lines 35-36 on page 75 of the PCT specification confirms that ztnf4 is a preferred ligand for BR43x2, TACI and BCMA. Binding of ztnf4 to TACI and BCMA is also illustrated in Figure 2 of the PCT specification.

Thus, there can be no doubt that the subject-matter "inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement" has basis in the PCT specification as filed, and hence amendment of the phrase "receptor-ligand engagement" to recite "receptor-ztnf4 engagement" does not add matter beyond the content of the application as filed.

Claims 13-28 as granted

8.3 In points 12-16 of the Statement of Grounds, Opponent I has alleged that Claims 13-

28 of the Patent as granted unallowably add subject-matter that extends beyond the content of the application as filed. These dependent "use" claims recite specific medical conditions that are treatable using the medicament of any of Claims 1 to 12 as granted. Claims 13-28 as granted correspond to published PCT Claims 10-28, and do not therefore add matter beyond the content of the application as filed.

8.4 Thus, Opponent I is incorrect to allege that the PCT specification as filed provides no basis for these specific therapeutic uses. In addition, we would refer the Opposition Division to at least the following passages from the PCT specification - page 53, lines 35-37; page 54, lines 27-36; page 55, line 1-page 57, line 11; and page 58, lines 3-10. Furthermore, treatment of systemic lupus erythematosis (SLE) is described in Example 13; treatment of ELE is described in Example 16; and treatment of rheumatoid arthritis is described in Example 17 of the PCT specification. It is thus evident that the PCT specification provides suitable basis for the specific therapeutic uses of Claims 13-28 as granted, and hence the subject-matter of these claims does not add matter beyond the content of the application as filed.

Claims 36-38 as granted

8.5 In points 17-19 of the Statement of Grounds, Opponent I has alleged that Claims 36-38 of the Patent as granted – relating to pharmaceutical compositions of antibodies – do not have adequate basis in the application as filed. The corresponding claims of Auxiliary Request 1 are Claims 24-26.

8.6 The PCT specification as filed (see, for example, method Claims 1 and 29) recites methods of medical treatment using antibodies. Hence, it would be implicit (if not explicit) to a skilled person that the PCT application as filed provides suitable basis for using antibodies to manufacture a medicament. Thus, it would also be evident that a claim to the end-product medicament also has basis in the PCT application as filed. In this regard, a skilled person would understand that the only way in which antibodies would be administered to a patient would be in the form of a pharmaceutical composition. By analogy, the PCT application as filed describes administration of polypeptides and antagonists (eg. antibodies) in the form of a pharmaceutical composition (see page 83, line 24 – page 84, line 19). Thus, the subject-matter of

Claims 24-26 as granted does not add matter beyond the content of the application as filed.

NOVELTY – ARTICLE 54 EPC AND ARTICLE 100a EPC

Novelty – Article 54(3) EPC

Claim 1h) as granted

8.7 In points 32-37 of the Statement of Grounds, Opponent I has alleged that Claim 1 of the Patent as granted lacks novelty in view of Master reference D3 (referred to as D2 by Opponent I). In particular, Opponent I has alleged that part h) of Claim 1 (as granted) is disclosed in D3. In this regard, Claim 1h) as granted corresponds to Claim 31 of Auxiliary Request 1.

8.8 Neither D3 nor its priority document (Master reference D20, referred to by Opponent I as D2a) discloses the subject-matter of Claim 31 of Auxiliary Request 1. D3 fails to disclose any of the specific medical conditions recited in Claim 31. In particular, there is no disclosure in D3 of using an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 8 for manufacture of a medicament for treating the specific medical conditions disclosed in Claim 31.

8.9 Thus, Claim 31 of Auxiliary Request 1 is novel over D3.

8.10 In points 38-44 of the Statement of Grounds, Opponent I has alleged that Claim 1h) of the Patent as granted (ie. Claim 31 of Auxiliary Request 1) lacks novelty in view of Master Reference citation D4 (referred to as D3 by Opponent I).

8.11 Neither D4 nor its priority document (Master reference D27, referred to by Opponent I as D3a) discloses the subject-matter of Claim 31 of Auxiliary Request 1. D4 fails to disclose any of the specific medical conditions recited in Claim 31. In particular, there is no disclosure in D4 of using an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 8 for manufacture of a medicament for treating the specific medical conditions disclosed in Claim 31.

8.12 Thus, Claim 31 of Auxiliary Request 1 is also novel over D4.

Claim 2 as granted

8.13 In points 45 and 46 of the Statement of Grounds, Opponent I has alleged that Claim 2 lacks novelty over Master reference citations D3 and D4 (referred to as D2 and D3 by Opponent I). Claim 2 as granted corresponds to dependent Claims 2 and 33 of Auxiliary Request 1.

8.14 Claim 2 of Auxiliary Request 1 depends on Claim 1. Claim 1 is novel over D3 and D4, which fail to disclose the compounds recited in Claim 1. Thus, Claim 2 is novel by virtue of dependency on novel Claim 1.

Claim 33 of Auxiliary Request 1 depends on any of Claims 27-32. D3 and D4 relate solely to BCMA, and do not disclose the compounds recited in Claims 27, 29-30 or 32. Hence, these claims are novel. With regard to Claims 28 and 31, there is no disclosure in D3 or D4 of using the recited compounds to treat the specific medical conditions recited in these claims, and hence Claims 28 and 31 are also novel. Thus, Claim 33 is novel over D3 and D4 by virtue of dependency on novel Claims 27-32.

Claim 3h) as granted

8.15 Opponent I has alleged, in points 47-50 of the Statement of Grounds, that Claim 3h) lacks novelty over Master references D3 and D4 (referred to by Opponent I as D2 and D3) for the same reasons as given with respect to Claim 1. Claim 3h) as granted corresponds to Claim 38 of Auxiliary Request 1.

8.16 Claim 38 of Auxiliary Request 1 is novel for the same reasons as given above with respect to Claim 31. In more detail, there is no disclosure in either D3 or D4 of using an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 8 for manufacture of a medicament for treating the specific medical conditions recited in Claim 38. Hence, Claim 38 is novel.

Claim 13 as granted

8.17 In points 51-55 of the Statement of Grounds, Opponent I has alleged that Claim 13 of the Patent as granted lacks novelty over Master references D3 and D4 (referred to by Opponent I as D2 and D3). The subject-matter of Claims 13-15 as granted is not claimed in Auxiliary Request 1 and hence these objections do not apply to Auxiliary Request 1.

Claims 16 and 17 as granted

8.18 In points 56 and 57 of the Statement of Grounds, Opponent I has alleged that Claims 16 and 17 of the Patent as granted lack novelty in view of Master Reference D3 (referred to by Opponent I as D2). The subject-matter of Claim 16 and 17 as granted has been incorporated into Claims 1, 3 and 32 of Auxiliary Request 1.

8.19 As discussed above, Claims 1, 3 and 32 of Auxiliary Request 1 are novel over D3, which relates to BCMA and fails to disclose any of the compounds recited in these claims.

Claim 19 as granted

8.20 In point 58 of the Statement of Grounds, Opponent I has alleged that Claim 19 of the Patent as granted - as it relates to "end stage renal failure" - lacks novelty in view of Master Reference D3 (referred to by Opponent I as D2), which allegedly describes treatment of "renal disorders". The "end stage renal failure" feature of Claim 19 as granted has been incorporated into Claims 1, 3, 28, 31, 32, 35, 38 and 39 of Auxiliary Request 1.

8.21 Claims 1, 3 and 32 are novel over D3 as discussed above. Claim 39 is also novel over D3, which fails to disclose the antibody/ antibody fragment recited in Claim 39. Claims 28, 31, 35 and 38 are novel over D3, which fails to disclose use of the recited compounds for any of the specific medical conditions recited in these claims. In this regard, the alleged disclosure of treating generic "renal disorders" in D3 is not an enabling disclosure of treating "end stage renal failure", which is a specific type of

renal disorder.

Claim 21 as granted

8.22 In point 59 of the Statement of Grounds, Opponent I has alleged that Claim 21 of the Patent as granted - as it relates to treatment of lymphomas - lacks novelty in view of Master Reference D3 (referred to by Opponent I as D2), which allegedly describes treatment of "lympho-proliferative disorders" (ie. lymphomas). The "lymphomas" feature of Claim 21 as granted has been incorporated into Claims 1, 3 and 32 of Auxiliary Request 1.

8.23 Claims 1, 3 and 32 are all novel over D3, as discussed above, since D3 fails to disclose any of the compounds recited in these claims.

Claim 27 as granted

8.24 In point 60 of the Statement of Grounds, Opponent I has alleged that Claim 27 of the Patent as granted lacks novelty in view of Master Reference D3 (referred to by Opponent I as D2). The subject-matter of Claim 27 as granted has been incorporated into Claims 1 and 3 of Auxiliary Request 1.

8.25 As discussed above, Claims 1 and 3 of Auxiliary Request 1 are novel over D3, which fails to disclose the novel compounds recited in these claims.

Claim 36 as granted

8.26 In points 61-64 of the Statement of Grounds, Opponent I has alleged that Claim 36 of the Patent as granted lacks novelty in view of Master references D3 and D4 (referred to by Opponent I as D2 and D3), which allegedly describe anti-BCMA antibodies. Claim 36 as granted corresponds to Claim 24 of Auxiliary Request 1.

8.27 Claim 24 of Auxiliary Request 1 is entitled to the 7 January 1999 priority date, which precedes the priority dates of D3 and D4 – hence, D3 and D4 are not citable against Claim 24 for novelty. In any case, Claim 24 of Auxiliary Request 1 does not recite any

anti-BCMA antibody and hence the objection raised by Opponent I no longer applies.

Claims 37 and 38 as granted

8.28 In points 65-67 of the Statement of Grounds, Opponent I has alleged that Claims 37 and 38 of the Patent as granted lack novelty in view of Master references D3 and D4 (referred to by Opponent I as D2 and D3), for the same reason as per Claim 36, above. Claims 37 and 38 as granted corresponds to Claims 25 and 26 of Auxiliary Request 1.

8.29 Claims 25 and 26 of Auxiliary Request 1 depend on independent Claim 24, which is novel over D3 and D4 as discussed above (paragraph 9.27). Furthermore, Claims 25 and 26 are entitled to the 7 January 1999 priority date, which precedes the D3 and D4 priority dates – hence, D3 and D4 are not citable against Claims 25 and 26 for novelty. Thus, Claims 25 and 26 of Auxiliary Request 1 are novel.

Novelty – Article 54(2) EPC

Claim 1 as granted

8.30 In points 70-71 of the Statement of Grounds, Opponent I has alleged that Claim 1 as granted lacks novelty over Master reference D1 (referred to by Opponent I as D5), which is alleged to disclose the use of anti-TACI antibodies for treatment of inflammatory diseases. The "anti-TACI antibody" aspects of Claim 1 as granted are now in Claim 30 of Auxiliary Request 1.

8.31 D1 fails to disclose using an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 6 for manufacture of a medicament for treating the specific medical conditions recited in Claim 30. In particular, the alleged generic disclosure in D1 of treating "inflammatory diseases" is not novelty-destroying of the specific forms of inflammation recited in Claim 30, namely "inflammation associated with joint pain, swelling or septic shock". Thus, Claim 30 is novel over D1.

Claim 3 as granted

8.32 In point 72 of the Statement of Grounds, Opponent I has alleged that Claim 3 as granted lacks novelty over Master reference D1 (referred to by Opponent I as D5), which is alleged to disclose the use of anti-TACI antibodies for treatment of inflammatory diseases. The "anti-TACI antibody" aspects of Claim 3 as granted are now to be found in Claim 37 of Auxiliary Request 1.

8.33 D1 does not disclose using an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 6 for manufacture of a medicament for treating the specific medical conditions recited in Claim 37. In particular, the alleged generic disclosure in D1 of treating "inflammatory diseases" does not destroy the novelty of the specific forms of inflammation recited in Claim 37 for treating "inflammation associated with joint pain, swelling or septic shock". Thus, Claim 37 is novel over D1.

8.34 In points 73 and 74 of the Statement of Grounds, Opponent I has alleged that part k) of Claim 3 as granted lacks novelty over Master reference D1 (referred to by Opponent I as D5), which is alleged to disclose the anti-human TACI antibodies. The "anti-SEQ ID NO: 20 antibodies" aspect of Claim 3 corresponds to Claim 3g) of Auxiliary Request 1.

8.35 D1 relates only to human TACI, and does not provide any specific disclosure of the murine TACI sequence SEQ ID NO: 20, which – as discussed in Master reference D37 – has only 54% identity to human TACI. In particular, there is no disclosure in D1 of an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 20, or of any use thereof as recited in Claim 3g) of Auxiliary Request 1. Thus, Claim 3g) is novel with respect to D1.

Claim 13-15 as granted

8.36 In points 75-77 of the Statement of Grounds, Opponent I has alleged that Claims 13-15 of the Patent as granted lack novelty in view of D1 (referred to by Opponent I as D5). The subject-matter of Claims 13-15 as granted is not claimed in Auxiliary Request 1, and hence these objections no longer apply.

Claims 16 and 17 as granted

8.37 In points 78-79 of the Statement of Grounds, Opponent I has alleged that Claims 16 and 17 of the Patent as granted lack novelty in view of D1 (referred to by Opponent I as D5). The subject-matter of Claims 16-17 as granted, namely use wherein the medicament is "for inhibiting antibody production associated with an autoimmune disease" is now found in Claims 1, 3 and 32 of Auxiliary Request 1.

8.38 As discussed above, Claims 1, 3 and 32 are novel over D1, which does not disclose the specific compounds of Claims 1 and 3 or the mechanism of action underlying Claim 32.

Claim 18 as granted

8.39 In point 80 of the Statement of Grounds, Opponent I has alleged that treatment of systemic lupus erythematosis, myasthenia gravis and rheumatoid arthritis using an anti-TACI antibody is known from D1 (referred to by Opponent I as D5). Thus Opponent I has alleged that Claim 18 of the Patent as granted lacks novelty over D1. The "systemic lupus erythematosis, myasthenia gravis and rheumatoid arthritis" aspects of Claim 18 of the Patent as granted are now found in Auxiliary Request 1 Claims 13, 28, 31, 35, 38 and 53 (see also Claim 39 which recites only myasthenia gravis).

8.40 Claim 13 of Auxiliary Request 1 is dependent (ultimately) on independent Claims 1 and 3, which, as discussed above, are novel over D1. Thus, Claim 13 is novel by virtue of dependency. D1 fails to disclose the compounds recited in Claims 28, 31, 35 and 38-39 of Auxiliary Request 1, and hence these claims are also novel. Claim 53 is dependent on Claim 32, which is novel over D1 as discussed above. Thus, Claim 53 is novel by virtue of dependency.

Claim 21 as granted

8.41 In point 81 of the Statement of Grounds, Opponent I has alleged that treatment of

myeloma and lymphoma using anti-TACI antibodies is disclosed in D1 (referred to by Opponent 1 as D5). Thus, Opponent 1 has alleged that Claim 21 of the Patent as granted lacks novelty over D1. The "myeloma and lymphoma" aspects of Claim 21 as granted are now to be found in Auxiliary Request 1 Claims 1, 3 and 32 (28, 31, 35 and 38 multiple myelomas only).

8.42 As discussed above, Claims 1 and 3 of Auxiliary Request 1 are novel over D1 by virtue of the novel compounds recited in these claims. Claim 32 is novel over D1, which does not disclose the specific mechanism of action underlying Claim 32. Claims 28, 31, 35 and 38 are also novel over D1, which fails to disclose any of the compounds used in these claims.

Claim 23 as granted

8.43 In point 82 of the Statement of Grounds, Opponent I has alleged that "moderating immune response" is known from D1 (referred to by Opponent 1 as D5). Thus, in Opponent I's opinion, Claim 23 of the Patent as granted lacks novelty over D1. The subject-matter of Claim 23 as granted is absent from Auxiliary Request 1, and hence this objection no longer applies.

Claims 27 and 28 as granted

8.44 In point 83 of the Statement of Grounds, Opponent I has alleged that Claims 27 and 28 of the Patent as granted lacks novelty in view of D1 (referred to by Opponent I as D5). The subject-matter of Claims 27 and 28 as granted, namely use of the medicament for the treatment of inflammation, in particular, inflammation associated with joint pain, swelling, anaemia or septic shock, is now found in Auxiliary Request 1 Claims 1, 3 and 16 (see also Claims 27-31 and 34-40, which recite treatment of inflammation associated with joint pain, swelling or septic shock only).

8.45 Claims 1 and 3 are novel over D1 as discussed above, by virtue of the specific compounds recited in these claims. Claim 16 is thus also novel by virtue of dependency on Claims 1 and 3. D1 also provides no disclosure of the compounds recited in Claims 28, 29, 31, 35-36, and 38-39 of Auxiliary Request 1 and hence these

claims are also novel. With regard to Claims 27, 30, 34 and 37 of Auxiliary Request 1 (which relate to TACI aspects of the present invention) D1 does not provide any explicit disclosure of treating inflammation associated with joint pain or swelling - which are specific types of inflammation, distinct from rheumatoid arthritis. Hence, Claims 27, 30, 34 and 37 of Auxiliary Request 1 are also novel over D1.

Claims 36-38 as granted

8.46 In point 84 of the Statement of Grounds, Opponent 1 has alleged that pharmaceutical compositions of anti-TACI antibodies as described in Claims 36-38 of the Patent as granted are known from D1. Claims 36-38 correspond to Claims 24-26 of Auxiliary Request 1.

8.47 As discussed above, D1 does not provide any explicit disclosure of an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 2, 4 or 10. As discussed above, it would be a matter of routine for a skilled person in the art to identify whether or not an antibody is "specifically binding". Hence these claims are novel over D1.

Claims 36 and 37 as granted

8.48 In points 85 and 86 of the Statement of Grounds, Opponent 1 has also alleged that Claims 36 and 37 of the Patent as granted lack novelty over Master reference D13 (referred to by Opponent I as D6). Claims 36 and 37 as granted correspond to Claims 24-25 of Auxiliary Request 1.

8.49 The antibodies or antibody fragments of pharmaceutical composition Claims 24-26 of Auxiliary Request 1 specifically bind to a polypeptide of SEQ ID NO: 2, 4 or 10. There is no disclosure in D13 of any of these polypeptides, let alone of antibodies that bind specifically to these polypeptides. Hence, these claims are novel over D1.

INVENTIVE STEP – ARTICLE 56 EPC AND ARTICLE 100a EPC

Claims 1 and 3 as granted

8.50 In point 87 of the Statement of Grounds, Opponent I has alleged that Claims 1 and 3 of the Patent as granted make no technical contribution to the art and thus lack an inventive step. In particular, Opponent I's inventive step allegation would appear to stem from their allegation that these claims do not recite any "defined, real treatment of any pathological condition".

8.51 Opponent I's allegation no longer applies to Auxiliary Request 1, in which the independent "use" claims all recite a number of defined, real medical conditions. Thus, independent "use" Claims 1, 3, 33-38 and 40-47 of Auxiliary Request 1 make a technical contribution to the art – namely, the provision of novel medicaments for treatment of specific medical conditions.

Closest Prior art and problem to be solved

8.52 In point 95 of the Statement of Grounds (after a brief discussion of the alleged background to the invention), Opponent I has alleged that Master reference D1 (referred to by Opponent I as D5) is the closest prior art to the Patent for assessment of inventive step.

8.53 In this regard, D1 relates only to TACI (and related compounds) and does not relate to BCMA or to BR43x2. Thus, D1 has only a limited relevance to inventive step of the claims of Auxiliary Request 1. This is particularly the case since D1 does not disclose any specific ligand for TACI, let alone the ligand ztnf4. Thus, in view of D1, many of the compounds recited in the claims of Auxiliary Request 1 would not be obvious to a skilled person. Furthermore, a skilled person reading D1 would not consider it obvious that the compounds recited in the "use" claims of Auxiliary Request 1 should (or even could) be used to inhibit ztnf4 activity or to inhibit BR43x2, TACI, or BCMA receptor-ztnf4 engagement. Hence, taking D1 as a starting point, all claims of Auxiliary Request 1 have an inventive step.

8.54 In point 97 of the Statement of Grounds, Opponent I has alleged that Master reference D12 (referred to by Opponent I as D7) is of relevance to inventive step of anti-BCMA aspects of the Patent. However, D12 is merely an academic publication

that fails to suggest treatment of any medical condition, let alone treatment of the very specific medical conditions recited in the claims of Auxiliary Request 1. Furthermore, there is no suggestion in D12 of inhibiting ztnf4 activity or inhibiting BR43x2, TACI, or BCMA receptor-ztnf4 engagement. Furthermore, with regard to antibodies, there is no suggestion in D12 of antibodies that would bind specifically to a polypeptide of SEQ ID NO: 8 (D12 fails to suggest any antibodies, and those produced by the D12 author and described in Master reference D13 are raised against a truncated BCMA–GST fusion protein). Hence, starting from D12, the claims of Auxiliary Request 1 have an inventive step.

8.55 Alternatively, in point 99 of the Statement of Grounds, Opponent I has suggested that Master reference D30 (referred to by Opponent I as D12) is the closest prior art. D30 does not, however, relate to BR43x2, TACI or BCMA and fails to suggest a single one of the compounds recited in the claims of Auxiliary Request 1. Furthermore, there is no suggestion whatsoever in D30 of inhibiting ztnf4 activity or inhibiting BR43x2, TACI, or BCMA receptor-ztnf4 engagement. Yet further, a skilled person reading D30 (which allegedly describes general "B-cell proliferative disorders") would not consider it obvious to treat the specific medical conditions recited in the claims of Auxiliary Request 1. Thus, the claims of Auxiliary Request 1 are inventive with respect to D30.

Claim 1g) as granted

8.56 In point 100 of the Statement of Grounds, Opponent I has alleged that the use of anti-TACI antibodies (part g of Claim 1 as granted) lacks an inventive step, in view of a combination of Master references D1, D6 and D5 (referred to by Opponent I as D5, D9 and D10, respectively). In this regard, Opponent I has alleged that it would have been obvious to identify ztnf4 as a ligand of TACI in view of Master references D5 and D6. Claim 1g) as granted corresponds to Claim 30 of Auxiliary Request 1.

8.57 D6 is not relevant to inventive step of the present invention since it fails to provide, or even suggest, the 264 amino acid sequence of ztnf4. Thus, even if D6 were to be combined with D1 this would not lead a skilled person towards the subject-matter of Claim 30, because both documents provide no suggestion of the ztnf4 ligand of the present invention. Thus, Claim 30 is inventive over a combination of D1 and D6.

8.58 Furthermore, a skilled person would not combine D1 with D5 since they relate to distinct molecules, which were not known to interact prior to the present invention. In particular, D1 recites that the endogenous ligand for TACI is not known (page 52, line 19); and no receptor for the ztnf4 sequence is suggested in D5. Thus a skilled person would have no reason to combine D1 and D5, and the combination of these documents by Opponent I is based, impermissibly, on hindsight.

8.59 Even if D1 and D5 were combined, their combined teaching would not lead a skilled person to Claim 30 of Auxiliary Request 1. In this regard, there is no suggestion in D1 that an anti-TACI antibody could be used to treat the specific medical conditions recited in Claim 30. Thus, Claim 30 of Auxiliary Request 1 is inventive with respect to D1, D5 and D6.

Claim 1h) as granted

8.60 In point 101 of the Statement of Grounds, Opponent I has alleged that the use of anti-BCMA antibodies (Claim 1h as granted) lacks an inventive step in view of a combination of Master references D1 and D12 (referred to by Opponent I as D5 and D7). Claim 1h) as granted corresponds to Claim 31 of Auxiliary Request 1.

8.61 Claim 31 of Auxiliary Request 1 is inventive with respect to a combination of D1 and D12, since there is no suggestion in either of these documents that would lead a skilled person to the claimed invention. In particular, neither of these documents suggests an antibody that specifically binds to a polypeptide of SEQ ID NO: 8. In more detail, D1 makes no reference whatsoever to BCMA and, in particular, provides no suggestion of any antibody that specifically binds to a polypeptide of SEQ ID NO: 8. With regard to D12, no antibodies are described in this paper, which relates primarily to characterisation of BCMA at the nucleic acid level. Thus, in view of D1 and D12, the recited antibody would not have been obvious.

8.62 Furthermore, there is no disclosure in D1 or D12 of the specific mechanism of action of the recited antibody, namely inhibition of ztnf4 activity. In this regard, there is no disclosure of any specific ligand, let alone ztnf4, in either D1 or D12. Thus, it would

not have been obvious to a skilled person reading these documents that an antibody that specifically binds to a polypeptide of SEQ ID NO: 8 could be used to inhibit ztnf4 activity. In particular, a combination of D1 and D12 would not lead a skilled person to expect that the recited antibody could be used to treat the specific medical conditions recited in Claim 31. This is particularly the case since the "BCMA" document D12 is merely academic in nature and fails to suggest any therapeutic uses. Thus, Claim 31 of Auxiliary Request 1 is inventive over D1 and D12.

Claim 1, parts g) and h) as granted

8.63 In point 102 of the Statement of Grounds, Opponent I has alleged that the use of anti-TACI and anti-BCMA antibodies (parts g and h of Claim 1) lacks an inventive step over a combination of Master reference D30 (referred to by Opponent I as D12) with Master reference D12, D1 or D9 (referred to by Opponent I as D7, D5 and D8, respectively). Claim 1g) as granted corresponds to Claim 30 of Auxiliary Request 1 and Claim 1h) as granted corresponds to Claim 31 of Auxiliary Request 1.

8.64 As discussed above, the disclosure of D30 is remote from the presently claimed invention, since there is no disclosure in D30 of an antibody that specifically binds to SEQ ID NO: 6 or 8. With regard to Claim 30, a combination of D30 with D12 would not make this claim obvious since there is no suggestion of anti-TACI antibodies in D12. A combination of D30 with D1 or D9 would also fail to suggest Claim 30, since neither D1 nor D9 provides any suggestion of any particular ligand for TACI, and hence provide no suggestion of inhibiting ztnf4 activity as claimed. Furthermore, neither D1 nor D9 suggests using an anti-SEQ ID NO: 6 antibody for manufacture of a medicament for treating the specific medical conditions recited in Claim 30. In this regard, D9 is a merely academic publication that provides no suggestion of any therapeutic application of anti-TACI antibodies, let alone their use for the specific therapies recited in Claim 30. Thus, Claim 30 of Auxiliary Request 1 has an inventive step over a combination of D30 with D12, D1 or D9.

8.65 With regard to Claim 31, a combination of D30 with D12 would not make this claim obvious since no antibodies are disclosed in D12. Furthermore, a combination of D30 with D1 or D9 would not lead a skilled person to Claim 31, since none of these

documents relate to BCMA, and in particular since none suggests any antibody that specifically binds to a polypeptide of SEQ ID NO: 8. Thus, Claim 31 of Auxiliary Request 1 is inventive over a combination of D30 with D12, D1 or D9.

Claim 2 as granted

8.66 In point 103 of the Statement of Grounds, Opponent I has alleged that Claim 2 of the Patent as granted lacks an inventive step in view of Master references D1 and D30. Claim 2 as granted corresponds to dependent Claims 2 and 33 of Auxiliary Request 1.

8.67 Claim 2 of Auxiliary Request 1 is inventive by virtue of dependency on Claim 1 of Auxiliary Request 1. Claim 1 is inventive over D1 and D30 since neither of these documents provides any suggestion of the compounds recited for use in Claim 1. In the light of D1, none of the BR43x2 aspects of Claim 1 would be considered obvious by a skilled person, who would predict that a biologically useful TACI isoform would comprise at least the first, highly conserved, cysteine rich pseudo repeat. In contrast, BR43x2 lacks this repeat, and yet unexpectedly retains high binding affinity for the ztnf4 ligand. There is no suggestion in D1 of BCMA, let alone the amino acid fragments of SEQ ID NO: 8 recited in parts f) and g) of Claim 1, and hence these aspects are inventive over D1. There is no suggestion in D1 of SEQ ID NO: 10 (the D1 consensus "Prosite" sequence is more broadly defined than SEQ ID NO: 10), and hence use of an antibody that specifically binds to a polypeptide having the more precise SEQ ID NO: 10 sequence would not have been obvious to a skilled person. Finally, there is no suggestion in D1 or D30 of any ligand molecule, let alone ztnf4, and hence inhibition of ztnf4 is inventive over D1 and D30. Thus, Claim 2 of Auxiliary Request 1, which incorporates all features of Claim 1, has an inventive step over D1 and D30.

8.68 Claim 33 of Auxiliary Request 1 is inventive by virtue of its dependency on any of Claims 27-32 of Auxiliary Request 1. As discussed above, Claims 30 and 31 are inventive over D1 and D30. Claims 28 and 29 are also inventive over D1 and D30, since neither of these documents provides any suggestion of the compounds recited for use in these claims. The use of a soluble polypeptide comprising the extracellular

domain of TACI as recited in Claim 27 of Auxiliary Request 1 would not be considered obvious by a skilled person in view of D1 or D30, as neither of these documents suggests any of the specific medical conditions recited in this claim. With regard to all of Claims 27-32, there is no suggestion in D1 or D30 of any specific ligand molecule, let alone ztnf4, and hence a skilled person reading D1 or D30 would not consider it obvious to use the recited compounds to inhibit ztnf4 activity. In contrast, the present inventors have identified that the recited compounds are useful for treating certain specific medical conditions, by a specific mechanism – namely inhibition of ztnf4 activity. Thus, Claims 27-32 are inventive over D1 and D30, and Claim 33 of Auxiliary Request 1 is inventive by dependency.

Claim 3g) as granted

8.69 In point 104 of the Statement of Grounds, Opponent I has alleged that the use of anti-TACI antibodies (part g) lacks an inventive step over Master reference D1 (referred to by Opponent I as D5). Claim 3g) as granted corresponds to Claim 37 of Auxiliary Request 1.

8.70 Opponent I is incorrect to allege that the D1 describes the use of "anti-TACI" antibodies to inhibit engagement of ztnf4 with the BR43x2, TACI or BCMA receptors. D1 is silent with regard to ztnf4 activity/ binding, and there is no suggestion in D1 that the D1 anti-TACI antibodies bind the TACI polypeptide at the ztnf4 binding site, or at any site that is involved in engagement with ztnf4, (thereby inhibiting the ability of ztnf4 to engage TACI).

8.71 Secondly, "inhibition of TACI", as described in D1, is not synonymous with inhibiting ztnf4 engagement, as presently claimed. In this regard, ztnf4 is one of a number of ligands that act through the TACI receptor, and inhibition of ztnf4 engagement represents an inventive selection from the possible ligand-TACI engagements that could be inhibited. Thus, since there is no suggestion of any specific ligand for the TACI receptor in D1, let alone ztnf4, it would not be obvious to a skilled person to use a specifically binding anti-SEQ ID NO: 6 antibody to inhibit BR43x2, TACI or BCMA receptor-ztnf4 engagement.

8.72 Furthermore, there is no suggestion in D1 of the specific therapeutic uses of the recited anti-SEQ ID NO: 6 antibody. In this regard, as discussed above, alleged general references in D1 to treating generalized conditions such as "autoimmune diseases" would not suggest to a skilled person that the recited antibody could be used to treat the specific medical conditions listed in Claim 37 of Auxiliary Request 1. In particular, there is no suggestion in D1 of treating these conditions by inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagements. Thus, Claim 37 of Auxiliary Request 1 is inventive over D1.

Claim 3h) as granted

8.73 In point 105 of the Statement of Grounds, Opponent I has alleged that the use of anti-BCMA antibodies (Claim 3h as granted) lacks an inventive step in view of a combination of Master references D1 and D12 (referred to by Opponent I as D5 and D7). Claim 3h) as granted corresponds to Claim 38 of Auxiliary Request 1.

8.74 Claim 38 of Auxiliary Request 1 is inventive with respect to a combination of D1 and D12, for the same reasons as given above with regard to Claim 1h) as granted. In particular, neither D1 nor D12 suggests an antibody that specifically binds to a polypeptide of SEQ ID NO: 8. In more detail, D1 does not relate to BCMA or suggest an antibody that specifically binds to a polypeptide of SEQ ID NO: 8. D12 fails to suggest any anti-BCMA antibodies. Thus, in view of D1 and D12, the recited antibody would not have been obvious.

8.75 Furthermore, there is no disclosure in D1 or D12 of the specific mechanism of action recited in Claim 38, namely inhibition of BR43x2, TACI or BCMA receptor-ztnf4 engagement. In this regard, neither D1 nor D12 discloses any specific ligand for these receptors, let alone ztnf4. Thus, it would not have been obvious to a skilled person reading D1 or D12 that engagement of ztnf4 with these receptors could be inhibited using an antibody that specifically binds to a polypeptide of SEQ ID NO: 8. In particular, it would not be obvious in view of a combination of D1 and D12 that the recited antibody could be used to treat the specific medical conditions recited in Claim 38. This is particularly the case since the "BCMA" document D12 is merely academic in nature and fails to suggest any therapeutic uses. Thus, Claim 38 of Auxiliary

Request 1 is inventive over D1 and D12.

Claim 3, parts g) and h) as granted

8.76 In point 106 of the Statement of Grounds, Opponent I has alleged that the use of anti-TACI and anti-BCMA antibodies (parts g and h) lacks an inventive step in view of a combination of Master reference D30 (referred to by Opponent I as D12) with Master reference D12, D1 or D9 (referred to by Opponent I as D7, D5 and D8, respectively). Claim 3g) as granted corresponds to Claim 37 of Auxiliary Request 1 and Claim 3h) as granted corresponds to Claim 38 of Auxiliary Request 1.

8.77 Claims 37 and 38 of Auxiliary Request 1 are inventive over D30, D12, D1 and D9 as discussed above with regard to Claims 30 and 31. In brief, D30 fails to suggest any antibody that specifically binds to SEQ ID NO: 6 or 8. Claim 37 is inventive over a combination of D30 with D12 since D12 fails to suggest anti-TACI antibodies. Claim 37 is also inventive over a combination of D30 with D1 or D9, since neither D1 nor D9 provides any suggestion of a specific ligand for TACI, and hence provide no suggestion of inhibiting receptor-ztnf4 engagements, as claimed. Furthermore, neither D1 nor D9 suggests treating the any of specific medical conditions recited in Claim 37. Thus, Claim 37 of Auxiliary Request 1 has an inventive step over a combination of D30 with D12, D1 or D9.

8.78 With regard to Claim 38, this claim is inventive over a combination of D30 with D12 since no antibodies are disclosed in D12. Furthermore, a combination of D30 with D1 or D9 would not lead a skilled person to Claim 38, since none of these documents relate to BCMA, and in particular does not suggest any antibody that specifically binds to a polypeptide of SEQ ID NO: 8. Thus, Claim 38 of Auxiliary Request 1 is inventive over a combination of D30 with D12, D1 or D9.

Claims 13-28 as granted

8.79 In point 108 of the Statement of Grounds, Opponent I has alleged that using an anti-TACI antibody to treat the specific medical conditions recited in Claims 13, 15-18, 21, 23, 27 and 28 of the Patent as granted lacks an inventive step in view of Master

reference D1 (referred to by Opponent I as D5). The subject-matter of Claims 13, 15 and 23 is absent from Auxiliary Request 1. The subject-matter of Claims 16-18, 21 and 27-28 is found in Claims 30 and 37 of Auxiliary Request 1.

8.80 Claims 30 and 37 are inventive over D1, which does not suggest treating any of the specific medical conditions recited in these claims. By way of example, general references in D1 to treating generalized conditions such as "inflammation" and "autoimmune diseases" would not suggest to a skilled person that the recited antibody could be used to treat the specific inflammatory and autoimmune conditions recited in Claims 30 and 37. In particular, a skilled person reading D1 would not think it obvious that these conditions could be treated by inhibiting of ztnf4 activity or receptor-ztnf4 engagements, since there is no suggestion of ztnf4 in D1.

8.81 In point 109 of the Statement of Grounds, Opponent I has alleged that, with regard to anti-BCMA antibodies, the subject-matter of these use claims also lacks an inventive step in view of a combination of Master reference D1 with Master reference D12. The "anti-BCMA antibody" use claims of Auxiliary Request 1 are Claims 31 and 38.

8.82 As discussed above with regard to Claims 30 and 37, Claims 31 and 38 are inventive over D1, which does not suggest treatment of any of the specific medical conditions that are recited in these claims. Furthermore, treatment of these conditions would not even be suggested by a combination of D1 with D12, which is a merely academic publication and fails to suggest any therapeutic uses. Moreover, D12 fails to suggest the use of any antibodies, let alone the specifically binding anti-SEQ ID NO: 8 antibodies recited in Claims 31 and 38. Thus, Claims 31 and 38 of Auxiliary Request 1 would not have been obvious in view of D1 and D12, and they have an inventive step.

8.83 In Point 110 of the Statement of Grounds, Opponent I has raised a specific inventive step objection against Claim 22 as granted, which relates to inhibiting effector T cells, in view of alleged prior art disclosures of activating B cells. In more detail, Opponent I has alleged that inhibition of effector T cells is an inherent consequence of activating certain types of B cells. The subject-matter of Claim 22 has been incorporated into Claims 1 and 3 of Auxiliary Request 1.

8.84 As discussed above, Claims 1 and 3 of Auxiliary Request 1 are both inventive since none of the cited prior art provides any suggestion of the compounds recited for use in these claims. Thus, it would not be obvious to use these compounds to inhibit effector T cells.

8.85 In point 111 of the Statement of Grounds, Opponent I has referred to Master reference D30 (referred to as D12 by Opponent I), which allegedly relates to using anti-B cell specific antibodies to treat lymphomas. The only claims of Auxiliary Request 1 that recite treatment of lymphomas are Claims 1, 3 and 32. These claims are all inventive over the cited prior art, which fails to suggest any of the specific compounds recited in Claims 1 and 3 of Auxiliary Request 1, or the specific mechanism of action underpinning Claim 32 of Auxiliary Request 1.

Claims 36-38 as granted

8.86 In point 112 of the Statement of Grounds, Opponent I has alleged that Claims 36-38 of the Patent as granted, in relation to anti-TACI and anti-BCMA antibodies, lack an inventive step in view of Master reference D1 (referred to by Opponent I as D5). Furthermore, in point 113 of the Statement of Grounds, Opponent I has also alleged that Claims 36-38 of the Patent as granted, in relation to anti-BCMA antibodies, lack an inventive step in view of Master reference D13 (referred to by Opponent I as D6). Claims 36-38 as granted correspond to Claims 24-26 of Auxiliary Request 1.

8.87 Neither D1 nor D13 provide any suggestion of the antibodies recited in parts a-c) of Claim 24 of Auxiliary Request 1. In particular, D1 and D13 both fail to suggest a polypeptide of SEQ ID NO: 2, 4 or 10, and hence a skilled person would not think it obvious to raise an antibody against these sequences. Hence, Claims 24-26 of Auxiliary Request 1 are inventive over D1 and D13.

Antibody or fragment that specifically binds to a polypeptide of SEQ ID NO: 10

8.88 In points 114-117 of the Statement of Grounds, Opponent I has alleged that Claims 1, 3 and 36 of the Patent as granted – to the extent to which they relate to an antibody or

fragment that specifically binds to SEQ ID NO: 10 – lack an inventive step. The subject-matter of these claims is found in Claims 1d), 3d) and 24c) of Auxiliary Request 1.

8.89 There is no suggestion in any of the cited prior art of an antibody that specifically binds to a polypeptide of SEQ ID NO: 10. In this regard, the "TACI" prior art documents cited for inventive step (D1 and D9) fail to suggest a polypeptide of SEQ ID NO: 10 (the "Prosite" consensus sequence provided in D1 is broader than SEQ ID NO: 10) and hence it would not be obvious to a skilled person to raise an antibody against this sequence. With regard to the citable "BCMA" prior art (D10-D13), the only antibodies suggested in these documents are raised against an N-terminally truncated BCMA polypeptide, which lacks part of the BCMA cysteine rich pseudo repeat. Thus, D10-D13 teach away from antibodies that specifically bind to a polypeptide of SEQ ID NO: 10. Thus, Claims 1d), 3d) and 24c) of Auxiliary Request 1 are inventive.

8.90 Furthermore, with regard to Claims 1d) and 3d), there is no suggestion in the cited prior art that an anti-SEQ ID NO: 10 antibody could be used therapeutically, let alone for treating the specific medical conditions recited in these claims. Moreover, there is no suggestion in the prior art that an anti-SEQ ID NO: 10 antibody could be used to inhibit ztnf4 activity, or to inhibit BR43x2m TACI or BCMA receptor-ztnf4 engagements, as claimed. Thus, Claims 1d) and 3d) of Auxiliary Request 1 have an inventive step.

SUFFICIENCY OF DISCLOSURE – ARTICLE 83 EPC AND ARTICLE 100c EPC

Claim 3 as granted

8.91 In points 118-120 of the Statement of Grounds, Opponent I has alleged that the subject-matter of Claim 3 as granted lacks sufficiency, insofar as it relates to TACI or BCMA receptor-ztnf4 engagement. In particular, Opponent I has alleged that the Patent specification does not enable a skilled person to selectively inhibit TACI or BCMA receptor-ztnf4 engagement (ie. without inhibiting the ability of TACI and BCMA to engage other ligands).

8.92 Opponent I is incorrect to take this view, since a skilled person would be aware that receptors that bind multiple ligands are common in the TNF receptor family (of which TACI, BCMA and BR43x2 are members). Furthermore, it would be understood by a skilled person that these receptors utilize distinct mechanisms in order to engage their different ligands. In this regard, we refer to Master reference D32, which provides an overview of the interactions between various TNF receptors (including TACI and BCMA) and their ligands (including ztnf4). It is evident from D32 that the various TNF ligands have different structures and thus two different ligands are likely to engage the same receptor in different ways. Thus, it would be immediately apparent to a skilled person that the engagement of ztnf4 with TACI or BCMA could be inhibited without inhibiting the engagement of any other ligand with these receptors.

8.93 This is confirmed by Master reference D33, which illustrates the different engagements that TACI and BCMA make with ztnf4 (=BAFF), as compared to a distinct ligand, APRIL. In this regard, it is apparent from Figure 2B (page 7221 of D33) that TACI engages APRIL and ztnf4 with different affinities (ztnf4 appears to bind with much lower affinity) – which is indicative of a different binding interaction between TACI and ztnf4 as compared to between TACI and APRIL. Thus, a skilled person would appreciate that it is possible to inhibit TACI-ztnf4 engagement without inhibiting TACI-APRIL engagement. No evidence to counter this has been provided by Opponent I.

8.94 Moreover, lines 7-12 of the right-hand column on page 7222 of D33 recite that mutation of a number of residues within the TACI polypeptide had an effect on binding of only one ligand – illustrating that TACI-ztnf4 engagements differ from TACI-APRIL engagements at an atomic level. Thus, these findings confirm that key TACI-ztnf4 interactions required for TACI-ztnf4 engagement may be inhibited without inhibiting binding of TACI to another ligand such as APRIL.

8.95 With regard to inhibiting BCMA-ztnf4 engagements, the first 2 paragraphs of the left-hand column on page 7225 of D33 recite that the interactions between BCMA and ztnf4 also differ at an atomic level from those between BCMA and APRIL. In more detail, BCMA residues 29-34 (within the BCMA cysteine-rich domain) make more

extensive interactions with APRIL than with ztnf4, which may account for the significantly higher affinity with which BCMA binds APRIL as compared to ztnf4. Furthermore, the BCMA polypeptide contacts regions in ztnf4 that are different in both sequence and conformation from the corresponding regions in APRIL. Thus, D33 confirms that BCMA-ztnf4 engagements differ considerably from BCMA-APRIL engagements, and it is therefore possible to inhibit BCMA-ztnf4 engagement without inhibiting BCMA-other ligand engagements by selective inhibition of the key receptor-ligand interactions.

8.96 With regard to Claim 39, and to parts e-f) of Claim 3 of Auxiliary Request 1, the antibodies recited in these claims are raised against the ztnf4 polypeptide (SEQ ID NO: 18), and against fragments of the ztnf4 polypeptide (SEQ ID NOs: 59 and 60), respectively. Hence, in use, these antibodies specifically bind to ztnf4 and thereby inhibit engagement of ztnf4 with its receptors, TACI and BCMA. Since these antibodies "specifically bind" to ztnf4, they would not (by definition) bind specifically to any other ligand, and hence would not inhibit engagement of any other ligand with TACI/ BCMA. Thus, use of these antibodies enables ztnf4 engagements to be inhibited without inhibiting the engagements of any other ligand.

8.97 Thus, with regard to TACI/BCMA-ztnf4 engagements, the subject-matter of Claim 3 as granted is sufficiently disclosed.

Claims 1 and 3 as granted

8.98 In points 121-123 of the Statement of Grounds, Opponent I has alleged that the Patent does not teach how to identify medical conditions that fall within the scope of Claims 1 and 3 as granted.

8.99 This objection does not apply to Auxiliary Request 1, in which the independent "use" claims recite specific medical conditions to be treated by the recited compounds.

Claim 36 as granted

8.100 In points 133-135 of the Statement of Grounds, Opponent I has alleged that there is

insufficient disclosure in the specification as filed of how to make and use medicaments that contain anti-BCMA or anti-TACI antibodies. In particular, Opponent I has alleged that any technical effect alleged in the Patent for these antibodies (especially anti-BCMA antibodies) is based on mere speculation.

8.101 "Pharmaceutical composition" Claim 24 of Auxiliary Request 1 does not recite anti-BCMA or anti-TACI antibodies, and hence Opponent I's allegation with respect to this claim no longer applies.

8.102 Claims 30, 31, 37 and 38 of Auxiliary Request 1 recite use of anti-SEQ ID NO: 6 and anti-SEQ ID NO: 8 antibodies for the manufacture of a medicament for inhibiting ztnf4 activity, or BR43x2, TACI or BCMA receptor-ztnf4 engagements, and thereby treating specific medical conditions. The recited antibodies are useful for these functions because they bind specifically to the TACI or BCMA receptor polypeptide and thereby prevent binding of ztnf4 to TACI or BCMA, respectively.

8.103 Contrary to Opponent I's allegations, it is not mere speculation to link this technical function to the recited specific medical conditions. In this regard, Example 5 of the Patent specification illustrates that human TACI and BCMA were identified in a number of tissues associated with the recited conditions. Furthermore, it is clear from Example 12 of the Patent specification that high levels of ztnf4 are associated with advanced stages of autoimmune disease (eg. the recited conditions SLE, myasthenia gravis, multiple sclerosis, rheumatoid arthritis and Crohn's disease). Thus, it is apparent from Example 12 of the Patent that using an anti-TACI or anti-BCMA antibody to inhibit the activity/ engagements of ztnf4 with TACI and/ or BCMA would be beneficial for treatment of autoimmune diseases.

8.104 This has been confirmed by Master reference D35 (recent PCT publication of the Proprietor), which describes, in Examples 1 and 2, the use of anti-TACI and anti-BCMA antibodies to inhibit the proliferation of multiple myeloma and lymphoma cells *in vitro* and *in vivo*.

8.105 Thus, the Patent specification provides sufficient disclosure of technical effects of the recited anti-TACI and ant-BCMA antibodies, and hence the subject-matter of Claim 36

as granted is sufficiently disclosed.

Antibodies that specifically bind to a polypeptide of SEQ ID NO: 10

8.106 In point 136 of the Statement of Grounds, Opponent I has alleged that antibodies (or fragments thereof) that bind to a polypeptide of SEQ ID NO: 10 are not sufficiently disclosed in the Patent. In particular, Opponent I has alleged that SEQ ID NO: 10 embraces a number of different antigens against which no described antibodies have been raised. This subject-matter is found in Claims 1 and 3 of Auxiliary Request 1.

8.107 SEQ ID NO: 10 represents a receptor polypeptide sequence containing 6 non-variable key cysteine residues that are involved in interactions with ligands (corresponding to residues 25, 40, 43, 47, 54 and 58 of the BR43x2 polypeptide - see paragraph 0019 of the Patent specification as granted). These 6 cysteine residues collectively form an important antigenic structure for generation of an anti-SEQ ID NO: 10 antibody that has the ability to inhibit ztnf4 activity/ engagements.

8.108 In this regard, Master reference D35 (by the Proprietor) describes antibodies that bind to a polypeptide of SEQ ID NO: 10. In particular, the monoclonal antibody 255.7 discussed in Examples 1-3 of D35 was raised against a polypeptide antigen having a sequence of SEQ ID NO: 10. As described in Example 1, this antibody was particularly useful for treatment of multiple myeloma, and was effective for inhibiting proliferation of Burkitt's lymphoma and multiple myeloma cell lines *in vitro*. Thus, D35 confirms that the antibodies of the Patent that specifically bind to a polypeptide of SEQ ID NO: 10 have the claimed biological activities.

SEQ ID NO: 20

8.109 In point 137 of the Statement of Grounds, Opponent I has alleged that the Patent does not sufficiently disclose the polypeptide of SEQ ID NO: 20, and hence that there is insufficient disclosure of an anti-SEQ ID NO: 20 antibody. Anti-SEQ ID NO: 20 antibodies are recited in Auxiliary Request 1 in Claim 3g.

8.110 The Opponent is incorrect to take this view since the polypeptide sequence of SEQ ID

NO: 20 is provided in the sequence listing on page 54-55 of the Patent specification. Given the polypeptide sequence, it would be routine for a skilled person to raise an antibody against this sequence. Furthermore, it would be routine for a skilled person to determine whether or not an antibody is "specifically binding" by determining the binding affinity (eg. by Scatchard analysis – see paragraph 0073 of the Patent specification). Hence, antibodies that specifically bind a polypeptide of SEQ ID NO: 20 are sufficiently disclosed in the Patent specification as filed.

9 OBSERVATIONS IN REPLY TO OPPONENT II

PATENTABILITY – ARTICLE 52(4) EPC AND ARTICLE 100a EPC

9.1 In points 42-45 of the Statement of Grounds, Opponent II has alleged that Claims 1-16 and 22-24 of the Patent as granted are unPatentable since - although drafted in 2nd medical use claim format – they allegedly are not directed to treatment of a specific therapeutic application.

9.2 Referring to Auxiliary Request 1, independent "second medical use" Claims 1, 3, 27-32 and 34-40 recite specific conditions/ diseases, and are therefore in a recognized "2nd medical use" claim format. Thus, the Opponent's objection no longer applies.

NOVELTY – ARTICLE 54 EPC AND ARTICLE 100a EPC

Novelty over Master reference D1

9.3 In point 53 of the Statement of Grounds, Opponent II has alleged that Master reference D1 (also referred to by Opponent II as D1) is prejudicial to novelty of Claims 1-16 and 22-24 of the Patent as granted. In this regard, Opponent II has interpreted these "use" claims as product *per se* claims in view of the above allegation of incorrect 2nd medical use format.

9.4 The Opponent's objection no longer applies to Auxiliary Request 1, in which all of the independent "2nd medical use" claims are in the recognised 2nd medical use claim format – ie. recite a real and defined medical condition to be treated.

Claims 1-12 as granted

9.5 In point 54 of the Statement of Grounds, Opponent II has alleged Claims 1-12 lack novelty in view of D1. The subject-matter of these claims is now to be found in Claims 1-12 and 27-52 of Auxiliary Request 1.

9.6 Claims 1-12 of Auxiliary Request 1 are novel with respect to D1, which does not recite

any of the compounds recited in independent base Claims 1 and 3. In more detail, D1 does not disclose any subject-matter relating to BR43x2 (parts a-c and e of Claim 1 and parts a-c and h of Claim 3); the ztnf4 ligand (parts e-f of Claim 3); BCMA (parts f-i of Claim 1 and parts i-l of Claim 3); murine TACI (part g of Claim 3); or SEQ ID NO: 10 (part d of Claims 1 and 3). With regard to part d of Claims 1 and 3, there is no disclosure in D1 of any antibody (or fragment thereof) that specifically binds to SEQ ID NO: 10. Thus, Claims 1 and 3, and hence all of Claims 1-12, are novel with respect to D1.

9.7 Independent Claims 28-29, 31, 35-36 and 38-39; and dependent Claims 42, 45 and 48 of Auxiliary Request 1 are also novel over D1, which does not recite the specific compounds used in these claims.

9.8 With regard to independent Claims 27, 30, 34, 37 and 40 of Auxiliary Request 1, these claims are also novel over D1, which does not disclose treatment of the specific medical conditions recited in these claims.

9.9 Claim 32 is novel over D1 by virtue of the mechanism of action of amino acid residues 1-166 of SEQ ID NO: 6, namely inhibiting ztnf4 activity. As discussed above, there is no disclosure in D1 of any specific ligand for TACI. In particular, there is no disclosure in D1 of ztnf4, let alone of inhibiting ztnf4 activity. Furthermore, D1 does not disclose that the specific medical conditions recited in Claim 32 of Auxiliary Request 1 are treatable by inhibiting ztnf4 activity using the amino acid residues 1-166 of SEQ ID NO: 6. In this regard, inhibiting ztnf4 is distinct from inhibiting TACI, and ztnf4 represents a selection from all the possible TACI ligands.

9.10 Thus, all the independent "use" claims of Auxiliary Request 1 are novel over D1, and hence all of Claims 1-12 and 27-52 of Auxiliary Request 1 are novel over D1.

Claims 13-15 as granted

9.11 In point 55 of the Statement of Grounds, Opponent II has alleged that Claims 13-15 of the Patent as granted lack novelty in view of D1. The subject-matter of Claims 13-15 is absent from Auxiliary Request 1, and hence Opponent II's objections do not apply

to Auxiliary Request 1.

Claim 16 as granted

9.12 In point 56 of the Statement of Grounds, Opponent II has alleged that Claim 16 of the Patent as granted lacks novelty in view of D1. The subject-matter of Claim 16 as granted is found in Claims 1, 3 and 32 of Auxiliary Request 1.

9.13 As discussed above, the compounds recited in Claims 1 and 3 of Auxiliary Request 1 are not disclosed in D1, and the specific mechanism of action recited in Claim 32 is not disclosed in D1. Hence, these claims are novel over D1.

Claim 22 as granted

9.14 In point 57 of the Statement of Grounds, Opponent II has alleged that Claim 22 of the Patent as granted lacks novelty in view of D1. The subject-matter of Claim 22 as granted, namely "inhibiting effector T cells" is found in Claims 1, 3, 28, 31, 32, 35 and 38 of Auxiliary Request 1.

9.15 As discussed above in more detail, the specific compounds recited in Claims 1, 3, 28, 31, 35 and 38; and the specific mechanism of action recited in Claim 32, are not disclosed in D1, and hence these claims are novel over D1.

Claim 17 as granted

9.16 In point 58 of the Statement of Grounds, Opponent II has alleged that Claim 17 of the Patent as granted lacks novelty in view of D1. The subject-matter of Claim 17 as granted, namely use of the medicament for inhibiting antibody production associated with an autoimmune disease is found in Claims 1, 3 and 32 of Auxiliary Request 1.

9.17 The compounds recited in Claims 1 and 3, and the mechanism of action recited in Claim 32 of Auxiliary Request 1, are not disclosed in D1, and hence these claims are novel over D1.

Claim 18 as granted

9.18 In point 59 of the Statement of Grounds, Opponent II has alleged that treatment of systemic lupus erythematosis, myasthenia gravis and rheumatoid arthritis is known from D1. Thus Opponent II has alleged that Claim 18 of the Patent as granted lacks novelty over D1. The "systemic lupus erythematosis, myasthenia gravis and rheumatoid arthritis" aspects of Claim 18 of the Patent as granted are now found in Auxiliary Request 1 Claims 13, 28, 31, 35, 38 and 53 (see also Claim 39 for myasthenia gravis).

9.19 Claim 13 of Auxiliary Request 1 is dependent (ultimately) on independent Claims 1 and 3, which, as discussed above, are novel over D1 by virtue of the recited compounds. Thus, Claim 13 is novel by way of dependency. Similarly, D1 does not disclose the compounds recited in Claims 28, 31, 35 and 38-39 of Auxiliary Request 1, and hence these claims are also novel. Claim 53 is dependent on Claim 32, which is novel over D1 by virtue of the recited mechanism of action, as discussed above. Thus, Claim 53 is novel by virtue of dependency.

Claims 19 and 20 as granted

9.20 In point 60 of the Statement of Grounds, Opponent II has alleged that D1 discloses treatment of glomerulonephritis and vasculitis, and is thus allegedly prejudicial to novelty of Claim 19 (end stage renal failure aspect) and Claim 20. The "end stage renal failure" aspect of Claim 19 as granted is found in Claims 1, 3, 28, 31, 32, 35 and 38-39 of Auxiliary Request 1, and the "glomerulonephritis and vasculitis" aspects of Claim 20 as granted are found in Claims 14 and 55 of Auxiliary Request 1.

9.21 All of independent Claims 1, 3, 28, 31, 32, 35 and 38-39 of Auxiliary Request 1 are novel over D1 by virtue of the specific compounds (Claims 1, 3, 28, 31, 35, 38 and 39), and the specific mechanism of action (Claim 32). Claim 14 is dependent (ultimately) on Claims 1 and 3 of Auxiliary Request 1 and is therefore novel by virtue of dependency. Claim 55 is dependent on any of novel claims 28, 31, 35 or 38 and is therefore novel by virtue of dependency.

Claim 21 as granted

9.22 In point 61 of the Statement of Grounds, Opponent II has alleged that Claim 21 of the Patent as granted, insofar as it relates to myeloma and lymphoma, lacks novelty in view of D1. The "myeloma and lymphoma" aspects of Claim 21 as granted are now found in Auxiliary Request 1 Claims 1, 3 and 32 (see also Claims 28, 31, 35 and 38 for multiple myelomas).

9.23 Claims 1 and 3 of Auxiliary Request 1 (by virtue of the recited compounds) and Claim 32 of Auxiliary Request 1 (by virtue of the specific mechanism of action) are novel over D1. Claims 28, 31, 35 and 38 are also novel over D1, which fails to disclose any of the compounds recited in these claims.

Claim 25 as granted

9.24 In point 62 of the Statement of Grounds, Opponent II has alleged that Claim 25 of the Patent as granted, insofar as it relates to immunosuppression associated with "graft rejection, graft versus host disease or autoimmune disease", lacks novelty in view of D1. These aspects of Claim 25 as granted are now to be found in Auxiliary Request 1 Claims 1, 3, 28, 31, 35 and 38.

9.25 Claims 1 and 3 of Auxiliary Request 1 are novel over D1, which does not disclose the compounds recited in these claims. For the same reasons, Claims 28, 31, 35 and 38 are also novel over D1.

Claims 27 and 28 as granted

9.26 In point 63 of the Statement of Grounds, Opponent II has alleged that Claims 27 and 28 of the Patent as granted lack novelty in view of D1. The subject-matter of Claims 27 and 28 as granted, namely use of the medicament for the treatment of inflammation, in particular, inflammation associated with joint pain, swelling, anaemia or septic shock, is now found in Auxiliary Request 1 Claims 1, 3 and 16 (see also Claims 27-31 and 34-40, which recite inflammation associated with joint pain, swelling or septic shock).

9.27 Claims 1 and 3 are novel over D1 by virtue of the recited compounds. Claim 16 is thus also novel by way of dependency on Claims 1 and 3. D1 fails to disclose the compounds recited in Claims 28, 29, 31, 35, 36, and 38-40 of Auxiliary Request 1 and hence these claims are also novel. With regard to Claims 27, 30, 34 and 37 of Auxiliary Request 1, there is no explicit disclosure in D1 of treating inflammation associated with joint pain or swelling - which are specific types of inflammation, distinct from rheumatoid arthritis. Hence, Claims 27, 30, 34 and 37 of Auxiliary Request 1 are also novel over D1.

Claims 36-38 as granted

9.28 In points 64-66 of the Statement of Grounds, Opponent II has alleged that Claims 36-38 of the Patent as granted lack novelty in view of D1, which allegedly discloses pharmaceutical compositions of anti-TACI antibodies. Claims 36-38 as granted correspond to Claims 24-26 of Auxiliary Request 1.

9.29 The antibodies or antibody fragments recited in Claims 24-26 of Auxiliary Request 1 specifically bind to SEQ ID NOs: 2, 4 or 10. There is no disclosure in D1 of antibodies (or fragments thereof) that bind specifically to the SEQ ID NOs recited in independent Claim 24, and hence Claim 24 is novel over D1. Dependent Claims 25-26 are novel by virtue of their dependency.

9.30 In more detail, contrary to the allegation of Opponent II, D1 does not disclose SEQ ID NO: 10 of the present invention. In this regard, the "Prosite" consensus sequence provided on pages 9 and 49 of D1 is more flexible than (ie. broader than) SEQ ID NO: 10 of the Patent. In particular, the D1 consensus sequence deviates widely from SEQ ID NO: 10 between the 5th and 6th Cys residues. Furthermore, D1 does not describe any antibody (or antibody fragment) that would bind specifically to SEQ ID NO: 10, as recited in part c) of Claim 24. In this regard, due to the considerable deviation between the D1 consensus sequence and SEQ ID NO: 10, it cannot be assumed that the D1 antibodies would bind specifically to SEQ ID NO: 10. Thus, Claim 24c) and dependent Claims 25-26 of Auxiliary Request 1 are novel over D1.

9.31 With regard to parts a) and b) of Claim 24, there is no disclosure in D1 of SEQ ID NOs: 2 or 4, let alone of any antibody that binds specifically to a polypeptide of SEQ ID NO: 2 or 4. Thus, Claims 24-26 of Auxiliary Request 1 are novel over D1.

Novelty over Master reference D9 (referred to by Opponent II as D2)

Claims 1-16 and 22-24 as granted

9.32 Opponent II's objections in point 71 of the Statement of Grounds no longer apply, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims should not be construed as product *per se* claims.

9.33 In point 72 of the Statement of Grounds, Opponent II has alleged that Claims 1-16 and 22-24 of the Patent as granted lack novelty over Master reference D9. The subject-matter of Claims 13-15 and 23 is absent from Auxiliary Request 1. The subject-matter of Claims 1-12, 16 and 23-24 as granted is to be found in Claims 1-12 and 27-52 of Auxiliary Request 1.

9.34 There is no disclosure in D9 of any of the compounds recited in independent base Claims 1 and 3, upon which Claims 2 and 4-12 depend. In more detail, D9 fails to disclose any subject-matter whatsoever relating to BR43x2; the ztnf4 ligand; BCMA; murine TACI, or SEQ ID NO: 10.

9.35 With regard to parts b) and c) of Claims 1 and 3, Opponent II is incorrect to assume that the antibodies described in D9 would specifically bind to the BR43x2 polypeptides of SEQ ID NO: 2 or 4. There is no enabling disclosure in D9 of SEQ ID NOs: 2 or 4, let alone of antibodies that bind specifically to a polypeptide of SEQ ID NO: 2 or 4, and hence Claim 1b) and c), and Claim 3 b) and c) are novel over D9.

With regard to part d) of Claims 1 and 3, D9 does not provide any disclosure of SEQ ID NO: 10, and in particular does not provide an enabling disclosure of any antibody (or fragment thereof) that specifically binds to SEQ ID NO: 10. In this regard, the D9 antibodies were raised against the N-terminal 151 amino acids of TACI (see note 10,

page 140 of D9), which is a much longer antigen than a polypeptide of SEQ ID NO: 10. Thus, the D9 antibodies raised against this TACI antigen would not bind specifically to SEQ ID NO: 10. Hence, Claims 1 and 3 are novel with respect to D9.

9.36 Thus, all of Claims 1-14 and 18-19 are novel over D9.

9.37 D9 also fails to disclose the subject-matter of Claims 27-52 of Auxiliary Request 1. In more detail, D9 does not disclose any of the compounds recited for use in independent base Claims 28-29, 31, 35-36 and 38-39 of Auxiliary Request 1, and hence these claims are novel over D9. With regard to independent Claims 27, 30, 34, 37 and 40 of Auxiliary Request 1, these claims are also novel over D9, which fails to disclose treatment of the specific medical conditions recited in these claims.

9.38 Claim 32 is novel over D9 by virtue of the mechanism of action of amino acid residues 1-166 of SEQ ID NO: 6, namely inhibiting ztnf4 activity. There is no disclosure in D9 of any ligand for TACI. In particular, there is no disclosure in D1 of ztnf4, let alone of inhibiting ztnf4 activity. Furthermore, D9 fails to disclose using amino acid residues 1-166 of SEQ ID NO: 6 for the manufacture of a medicament for treating any medical condition by inhibiting ztnf4 activity, let alone the specific medical conditions recited in Claim 32.

9.39 Thus, all "use" claims of Auxiliary Request 1 are novel over D9.

Claims 36 and 37 as granted

9.40 In points 73-74 of the Statement of Grounds, Opponent II has alleged that Claims 36 and 37 of the Patent as granted lack novelty over D9. Claims 36 and 37 as granted correspond to Claims 24 and 25 of Auxiliary Request 1.

9.41 The antibodies and antibody fragments recited in Claim 24 of Auxiliary Request 1 specifically bind to SEQ ID NOs: 2, 4 or 10. There is no disclosure in D9 of any of these SEQ ID NOs, let alone of antibodies (or fragments thereof) that bind specifically to these SEQ ID NOs.

9.42 With regard to parts a) and b) of Claim 24, the D9 antibodies were raised against the 151 N-terminal amino acids of TACI, which is a distinct antigen from a polypeptide of SEQ ID NO: 2 or 4. Hence, the D9 antibodies would not bind specifically to a polypeptide of SEQ ID NO: 2 or 4. In this regard, a skilled person would be able to identify a specifically binding antibody as a matter of routine, as discussed in paragraph 0073 of the Patent. Hence, Claim 24a) and b) is novel over D1, and dependent Claim 25 is novel by virtue of dependency.

9.43 Turning now to part c) of Claim 24, contrary to the Opponent II's allegation, D9 does not explicitly disclose SEQ ID NO: 10 of the present invention. Furthermore, D9 does not explicitly disclose any antibody (or antibody fragment) that would bind specifically to SEQ ID NO: 10. In this regard, the D9 antibodies were raised against the 151 N-terminal amino acids of TACI, which represents most of the TACI extracellular domain and in particular is a distinct antigen from a polypeptide of SEQ ID NO: 10. Thus, the D9 antibodies would not bind specifically to a polypeptide of SEQ ID NO: 10 (see paragraph 0073 of the Patent specification for a definition of "specifically binding"). Hence, Claims 24 and 25 of Auxiliary Request 1 are novel over D9.

Novelty over Master reference D11 (referred to by Opponent II as D3)

Claims 1-16 and 22-24 as granted

9.44 Opponent II's objections in point 78 of the Statement of Grounds no longer apply, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims should not be construed as product *per se* claims.

9.45 In point 79 of the Statement of Grounds, Opponent II has alleged that Claims 1-16 and 22-24 of the Patent as granted lack novelty over Master reference D11. The subject-matter of Claims 13-15 and 23 is absent from Auxiliary Request 1. The subject-matter of Claims 1-12, 16, 22 and 24 as granted is to be found in Claims 1-12 and 27-52 of Auxiliary Request 1.

9.46 Independent Claims 1 and 3, upon which Claims 2 and 4-12, are novel over D11. In

more detail, D11 fails to disclose BR43x2 (parts a-c and e of Claim 1 and parts a-c and h of Claim 3); the ztnf4 ligand (parts e-f of Claim 3); BCMA (parts f-i of Claim 1 and parts i-l of Claim 3); murine TACI (part g of Claim 3); or SEQ ID NO: 10 (part d of Claims 1 and 3).

9.47 With regard to part d) of Claims 1 and 3 - as acknowledged by Opponent II in point 77 of the Statement of Grounds - D11 fails to provide any consensus sequence, let alone the particular sequence of SEQ ID NO: 10. Furthermore, there is no enabling disclosure in D11 of any antibody (or antibody fragment) that would bind specifically to SEQ ID NO: 10, as recited in part d) of Claims 1 and 3. Thus, Claims 1d) and 3d) are novel over D11.

9.48 D11 also fails to disclose the subject-matter of Claims 27-52 of Auxiliary Request 1. In particular, D11 does not disclose any of the compounds recited for use in independent base Claims 27, 30, 32, 34, 37 or 39-40, and hence these claims, and all claims dependent thereon, are novel over D11. With regard to Claims 28-29, 31, 35-36 and 38 of Auxiliary Request 1, D11 is merely an academic publication and fails to disclose the specific medical conditions recited in these claims. Thus, these claims and all claims dependent thereon are novel over D11.

9.49 Thus, all of Claims 1-12 and 27-52 are novel over D11.

Claim 36 as granted

9.50 In point 80 of the Statement of Grounds, Opponent II has alleged that Claim 36 of the Patent as granted lacks novelty over D11 – which is alleged to disclose antibodies that bind to BCMA and antibodies that bind to SEQ ID NO: 10. Claim 36 corresponds to Claim 24 of Auxiliary Request 1.

9.51 The antibodies and antibody fragments recited in parts a-c) of Claim 30 are not disclosed in D11. In this regard, D11 fails to disclose any antibody that specifically binds to a BR43x2 polypeptide of SEQ ID NO: 2 or SEQ ID NO: 4. In addition, D11 fails to provide sufficient disclosure of any antibody that would bind specifically to the consensus sequence SEQ ID NO: 10. Thus, Claim 24 is novel over D11.

Novelty over Master reference D13 (referred to by Opponent II as D4)

Claims 1-16 and 22-24 as granted

9.52 Opponent II's objections in point 84 of the Statement of Grounds no longer apply, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims should not be construed as product *per se* claims.

9.53 In point 79 of the Statement of Grounds, Opponent II has alleged that Claims 1-16 and 22-24 of the Patent as granted lack novelty over Master reference D13. The subject-matter of Claims 13-15 and 23 is absent from Auxiliary Request 1. The subject-matter of Claims 1-12, 16, 22 and 24 as granted is to be found in Claims 1-12 and 27-52 of Auxiliary Request 1.

9.54 Independent Claims 1 and 3, upon which Claims 2 and 4-12 depend, are novel over D13. In more detail, D13 fails to disclose BR43x2 (parts a-c and e of Claim 1 and parts a-c and h of Claim 3); the ztnf4 ligand (parts e-f of Claim 3); BCMA (parts f-i of Claim 1 and parts i-l of Claim 3); murine TACI (part g of Claim 3); or SEQ ID NO: 10 (part d of Claims 1 and 3).

9.55 With regard to part d) of Claims 1 and 3, D13 provides no sequence data, but merely refers to the sequences of D11. As discussed above, there is no disclosure in D11 of the consensus sequence SEQ ID NO: 10. Furthermore, there is no enabling disclosure in D11 or D13 of any antibody (or antibody fragment) that would bind specifically to SEQ ID NO: 10, as recited in part d) of Claims 1 and 3. Thus, Claims 1d) and 3d) are novel over D13.

9.56 D13 also fails to disclose the subject-matter of Claims 27-52 of Auxiliary Request 1. In particular, D13 does not disclose any of the compounds recited in independent base Claims 27, 30, 32, 34, 37 or 29-40, and hence these claims, and all claims dependent thereon, are novel over D13. D13 provides no disclosure of any of the specific medical conditions recited in Claims 28-29, 31, 35-36 and 38 of Auxiliary

Request 1. Thus, these claims and all claims dependent thereon are novel over D13.

9.57 Thus, Claims 1-12 and 27-52 are all novel over D13.

Claims 36 and 37 as granted

9.58 In points 86-87 of the Statement of Grounds, Opponent II has alleged that Claims 36 and 37 of the Patent as granted lack novelty over D13 – which is alleged to disclose antibodies that bind to BCMA and antibodies that bind to SEQ ID NO: 10. Claims 36 and 37 correspond to Claims 24 and 25 of Auxiliary Request 1.

9.59 D13 does not disclose the antibodies or antibody fragments recited in parts a-c) of Claim 30. In more detail, there is no disclosure in D13 of any antibody that specifically binds to a BR43x2 polypeptide of SEQ ID NO: 2 or SEQ ID NO: 4. In addition, D13 fails to provide a sufficient disclosure of any antibody that would bind specifically to the consensus sequence SEQ ID NO: 10. Thus, Claim 24 is novel over D13 and Claim 25 is novel by dependency.

Novelty over Master reference D12 (referred to by Opponent II as D5)

Claims 1-16 and 22-24 as granted

9.60 Opponent II's objections in point 91 of the Statement of Grounds no longer apply, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims should not be construed as product *per se* claims.

9.61 In point 92 of the Statement of Grounds, Opponent II has alleged that Claims 1-16 and 22-24 of the Patent as granted lack novelty over Master reference D12. The subject-matter of Claims 13-15 and 23 is absent from Auxiliary Request 1. The subject-matter of Claims 1-16, 22 and 24 as granted is to be found in Claims 1-12 and 27-52 of Auxiliary Request 1.

9.62 Independent Claims 1 and 3, upon which Claims 2 and 4-12 depend, are novel over

D12. In more detail, D12 fails to disclose BR43x2; the ztnf4 ligand; BCMA or murine TACI. Furthermore, with regard to part d) of Claims 1 and 3, there is no enabling disclosure in D12 of any antibody/ antibody fragment that would bind specifically to the consensus sequence SEQ ID NO: 10. Thus, Claims 1 and 3 are novel over D12.

9.63 D12 also fails to disclose the subject-matter of Claims 27-52 of Auxiliary Request 1. In particular, D12 does not disclose any of the compounds recited in independent base Claims 27, 30, 32, 34, 37 or 39-40, and hence these claims, and all claims dependent thereon, are novel over D12. D12 provides no disclosure of any of any specific medical conditions, let alone the specific medical conditions recited in Claims 34-35, 37, 41-42 and 44 of Auxiliary Request 1. Thus, these claims and all claims dependent thereon are novel over D12.

9.64 Thus, Claims 1-12 and 27-52 of Auxiliary Request 1 are novel over D12.

Novelty over Master reference D5 (referred to by Opponent II as D6)

Claims 3-16 and 22-24 as granted

9.65 Opponent II's objections in point 97 of the Statement of Grounds no longer apply, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims should not be construed as product *per se* claims.

Claim 3 as granted

9.66 In point 98 of the Statement of Grounds, Opponent II has alleged that Claim 3 of the Patent as granted lacks novelty in view of D5. The subject-matter of Claim 3 as granted is now to be found in Claims 3 and 34-40 of Auxiliary Request 1.

9.67 Claim 3 of Auxiliary Request 1 is novel over D5, which fails to disclose any of the compounds specifically recited in Claim 3. In particular, there is no enabling disclosure in D5 of using any antibody that binds specifically to a polypeptide of SEQ ID NO: 59 or 60, as recited in parts e) and f), respectively, of Claim 3.

9.68 D5 also fails to disclose any of the compounds recited in Claims 34-38 or 40 of Auxiliary Request 1, and hence these claims are also novel over D5.

9.69 With regard to Claim 39 of Auxiliary Request 1, this claim is also novel over D5, which fails to disclose any of the specific medical conditions recited in Claim 39.

Claims 4-12 as granted

9.70 In point 99 of the Statement of Grounds, Opponent II has alleged that Claims 4-12 of the Patent as granted lack novelty over D5, to the extent that they relate to fusions containing the ztnf4 fragment SEQ ID NO: 18. Claims 4-12 as granted correspond to Claims 4-12 and 41-52 of Auxiliary Request 1.

9.71 Claims 4-12 of Auxiliary Request 1 all depend (ultimately) on either of novel independent base Claims 1 and 3, and hence Claims 4-12 are novel over D5 by virtue of this dependency.

9.72 Claims 41-52 of Auxiliary Request 1 depend (ultimately) on any of Claims 27, 29, 32, 34, 36, or 40; or on any of Claims 28-29 or 35-36. None of the compounds recited in these base claims is disclosed in D5 and, in particular, there is no disclosure in D5 of any fusion proteins comprising any of the sequences recited in Claims 41-47 (none of which are ztnf4 sequences). Thus, Claims 41-52 of Auxiliary Request 1 are novel over D5.

Claims 13-15 as granted

9.73 In point 100 of the Statement of Grounds, Opponent II has alleged that D5 discloses using anti-ztnf4 antibodies to treat B lymphocytes. Hence, Opponent II has alleged that Claims 13-15 of the Patent as granted lack novelty over D5. The subject-matter of Claims 13-15 as granted is absent from Auxiliary Request 1.

Claims 22-24 as granted

9.74 In point 101 of the Statement of Grounds, Opponent II has alleged that Claims 22-24 of the Patent as granted lack novelty over D5. Whilst the subject-matter of Claim 23 is not present in Auxiliary Request 1, the subject-matter of Claims 22 and 24 as granted is to be found in Claims 1, 3, 28, 31-32, 35 and 38 of Auxiliary Request 1.

9.75 As discussed above, Claims 1 and 3 of Auxiliary Request 1 are novel over D5 by virtue of the recited compounds. With regard to Claims 28, 31-32, 35 and 38, none of the compounds recited for use in these claims is disclosed in D5 and hence these claims are novel over D5.

Claim 17 as granted

9.76 In point 102 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 17 of the Patent as granted is disclosed in D5. Claim 17 as granted corresponds to Claims 1, 3 and 32 of Auxiliary Request 1.

9.77 Claims 1, 3 and 32 are novel over D5 by virtue of the recited compounds, as discussed above.

Claim 18 as granted

9.78 In point 103 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 18 of the Patent as granted - insofar as it relates to multiple sclerosis or rheumatoid arthritis - is disclosed in D5. The "multiple sclerosis" and "rheumatoid arthritis" aspects of Claim 18 as granted are found in Claims 13, 28, 31, 35, 38, and 53 of Auxiliary Request 1.

9.79 Claim 13 of Auxiliary Request 1 is dependent (ultimately) on any of Claims 1 and 3, which as discussed above are novel over D5 by virtue of the recited compounds. Thus, Claim 13 is also novel, by dependency. Also as discussed above, Claims 28, 31, 35 and 38 are novel over D5, which fails to disclose any of the compounds recited in these claims. Claim 53 is novel by dependency on Claim 32, which in turn is also novel over D5 by virtue of the recited compound.

Claim 19 as granted

9.80 In point 104 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 19 of the Patent as granted - insofar as it relates to asthma - is disclosed in D5. The "asthma" aspects of Claim 19 as granted are found in Claims 1, 3, 27-31, 34-38 and 40 of Auxiliary Request 1.

9.81 As discussed above, the molecules recited in Claims 1 and 3 of Auxiliary Request 1 establish novelty over D5. Claims 27-31, 34-38 and 40 of Auxiliary Request 1 are also novel over D5, which fails to disclose any of the compounds recited in these claims.

Claim 21 as granted

9.82 In point 105 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 21 of the Patent as granted is disclosed in D5. The subject-matter of Claim 21 as granted is found in Claims 1, 3, 27-32 and 34-40 of Auxiliary Request 1.

9.83 D5 fails to disclose the compounds recited in Claims 1, 3, 27-32 and 34-38 and 40 of Auxiliary Request 1, and hence these claims are novel over D5. With regard to Claim 39 of Auxiliary Request 1, the general teaching in D5 of treating "tumours" does not provide an enabling disclosure of treating "renal neoplasms, light chain neuropathy or amyloidosis". Thus, Claim 39 of Auxiliary Request 1 is also novel over D5.

Claim 25 as granted

9.84 In point 106 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 25 of the Patent as granted - insofar as it relates to immunosuppression associated with autoimmune disease or inflammation - is disclosed in D5. These aspects of Claim 25 as granted are found in Claims 1, 3, 28, 31, 35 and 38 of Auxiliary Request 1, which are all novel over D5 by virtue of the recited compounds, as discussed above.

Claim 26 as granted

9.85 In point 107 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 26 of the Patent as granted - insofar as it relates to insulin dependent diabetes mellitus – lacks novelty in view of D5. The "diabetes" aspect of Claim 26 as granted is now found in Claims 15 and 54 of Auxiliary Request 1.

9.86 Claim 15 of Auxiliary Request 1 is dependent (ultimately) on either of Claims 1 or 3, which as discussed above are novel over D5 by virtue of the recited compounds. Thus, Claim 15 is also novel over D5, by way of its dependency. Claim 54 of Auxiliary Request 1 depends (ultimately) on Claim 32, which also is novel over D5 by virtue of the recited compound. Thus, Claim 54 is also novel over D5.

Claims 27 and 28 as granted

9.87 In point 108 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claims 27 and 28 of the Patent as granted - insofar as they relate to inflammation associated with joint pain or anaemia - lack novelty over D5. The subject-matter of Claim 27 and Claim 28 (joint pain or anaemia) has been incorporated into Claims 1, 3, 16, 27-31 and 34-40 of Auxiliary Request 1.

9.88 D5 fails to disclose the compounds recited for use in Claims 1, 3, 27-31, 34-38 and 40 of Auxiliary Request 1, and hence these claims are all novel over D5. Claim 16 is novel over D5 by virtue of its dependency on novel Claims 1 or 3. With regard to Claim 39, the description in D5 of treating rheumatoid arthritis does not provide an enabling disclosure of treating inflammation associated with joint pain or swelling. Thus, Claim 39 is novel over D5.

Novelty over Master reference D6 (referred to by Opponent II as D7)

Claims 3-16 and 22-24 as granted

9.89 Opponent II's objections in point 112 of the Statement of Grounds no longer apply, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims

should not be construed as product *per se* claims.

Claim 3 as granted

9.90 In point 113 of the Statement of Grounds, Opponent II has alleged that Claim 3 of the Patent as granted lacks novelty in view of D6. The subject-matter of Claim 3 as granted is now to be found in Claims 3 and 34-40 of Auxiliary Request 1.

9.91 Claim 3 of Auxiliary Request 1 is novel over D6, which fails to disclose any of the compounds specifically recited in Claim 3. In this regard, there is no enabling disclosure in D6 of using any antibody that binds specifically to a polypeptide of SEQ ID NO: 59 or 60, as recited in parts e) and f), respectively, of Claim 3.

9.92 D6 also fails to disclose any of the compounds recited in Claims 34-38 or 40 of Auxiliary Request 1, and hence these claims are also novel over D6.

9.93 With regard to Claim 39 of Auxiliary Request 1, this claim is also novel over D6, which fails to explicitly disclose the sequence of SEQ ID NO: 18. In this regard, the D6 ligand sequence is 285 amino acids long, whereas SEQ ID NO: 18 of the Patent is only 264 amino acids long (corresponding to amino acid residues 22-285 of the D6 sequence). Furthermore, there is no enabling disclosure in D6 of any antibody that binds specifically to SEQ ID NO: 18 of the Patent, and Opponent II is incorrect to assume that antibodies raised against SEQ ID NO: 2 of D6 would bind specifically to the short ligand sequence SEQ ID NO: 18. Thus, Claim 39 is novel over D6.

9.94 Furthermore, Claim 39 is also novel over D6 since there is no disclosure in D6 of any of the specific medical conditions recited in Claim 39.

Claims 4-12 as granted

9.95 In point 114 of the Statement of Grounds, Opponent II has alleged that "fusion protein" Claims 4-12 of the Patent as granted - insofar as the fusions contain the ztnf4 fragment SEQ ID NO: 18 - lack novelty in view of D6. The subject-matter of Claims 4-12 as granted is now to be found in Claims 4-12 and 41-52 of Auxiliary Request 1.

9.96 None of Claims 4-12 or 41-52 of Auxiliary Request 1 recite a fusion protein in which the first portion comprises the ztnf4 fragment SEQ ID NO: 18. Furthermore, all of the claimed fusions comprise polypeptides containing a BR43x2, TACI or BCMA amino acid sequence. None of these sequences are disclosed in D6, and hence Claims 4-12 and 41-52 of Auxiliary Request 1 are novel over D6.

Claim 17 as granted

9.97 In point 115 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 17 of the Patent as granted is disclosed in D6. Claim 17 as granted corresponds to Claims 1, 3 and 32 of Auxiliary Request 1, which as discussed above, are all novel over D6.

Claim 18 as granted

9.98 In point 116 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 18 of the Patent as granted - insofar as it relates to rheumatoid arthritis - is disclosed in D6. The "rheumatoid arthritis" aspect of Claim 18 as granted is found in Claims 13, 28, 31, 35, 38, and 53 of Auxiliary Request 1.

9.99 Claim 13 of Auxiliary Request 1 is dependent (ultimately) on any of Claims 1 and 3, which as discussed above are novel over D6 by virtue of the recited compounds. Thus, Claim 13 is also novel, by dependency. Claims 28, 31, 35 and 38 are novel over D6, which fails to disclose any of the compounds recited in these claims. Claim 53 is dependent on Claim 32, which is also novel over D6, since D6 does not disclose amino acids 1-166 of SEQ ID NO: 6. Thus, Claim 53 is novel over D6 by virtue of dependency.

Claim 21 as granted

9.100 In point 117 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 21 of the Patent as granted is disclosed in D6. The subject-matter of Claim 21 as granted is found in Claims 1, 3, 27-32 and 34-40 of Auxiliary Request 1.

9.101 As discussed above, D6 fails to disclose the any of the compounds recited in Claims 1, 3, 27-32 and 34-40 of Auxiliary Request 1, and hence these claims are novel over D6. Furthermore, with regard to Claim 39 of Auxiliary Request 1, the general teaching in D6 of treating "cancers" (and specifically lympho-proliferative disorders) does not provide an enabling disclosure of the specific conditions "renal neoplasms, light chain neuropathy or amyloidosis". Thus, Claim 39 of Auxiliary Request 1 is also novel over D6.

Claim 25 as granted

9.102 In point 118 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 25 of the Patent as granted - insofar as it relates to immunosuppression associated with graft rejection or graft versus host disease - is disclosed in D6. These aspects of Claim 25 as granted are found in Claims 1, 3, 28, 31, 35 and 38 of Auxiliary Request 1, which are all novel over D6 as discussed above by virtue of the recited compounds.

Claim 26 as granted

9.103 In point 119 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claim 26 of the Patent as granted - insofar as it relates to Crohn's Disease lacks novelty in view of D6. The "Crohn's Disease" aspect of Claim 26 as granted is now found in Claims 15, 27, 29-30, 34, 36-37, 39-40 and 54 of Auxiliary Request 1.

9.104 Claim 15 of Auxiliary Request 1 is dependent (ultimately) on either of Claims 1 or 3, which as discussed above are novel over D6. Thus, Claim 15 is also novel over D6, by way of its dependency. Claim 54 of Auxiliary Request 1 depends (ultimately) on Claim 32, which is also novel over D6 as discussed above, by virtue of the recited compound. Thus, Claim 54 is novel over D6 by way of dependency. Claims 27, 29-30, 34, 36-37 and 39-40 are all novel over D6, which fails to disclose the specific compounds recited in these claims. Furthermore, with regard to Claim 39 of Auxiliary Request 1, the generic disclosure in D6 of treating "inflammatory bowel diseases" does not provide an enabling disclosure of treating the specific medical condition

Crohn's Disease. Hence, Claim 39 is novel over D6.

Claims 27 and 28 as granted

9.105 In point 120 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claims 27 and 28 of the Patent as granted - insofar as they relate to inflammation associated with joint pain or swelling - lack novelty over D6. The subject-matter of Claim 27 and Claim 28 (joint pain or swelling) has been incorporated into Claims 1, 3, 16, 27-31 and 34-40 of Auxiliary Request 1.

9.106 D6 fails to disclose the compounds recited for use in Claims 1, 3, 27-31 and 34-40 of Auxiliary Request 1, and hence these claims are all novel over D6. Furthermore, with regard to Claim 39, the description in D6 of treating rheumatoid arthritis does not destroy novelty of treating inflammation associated with joint pain or swelling – these are distinct medical conditions. Thus, Claim 39 is novel over D6. Claim 16 is novel over D6 by virtue of its dependency on novel Claims 1 or 3.

Novelty over Master reference D15 (referred to by Opponent II as D8)

Claims 3-16 and 22-24 as granted

9.107 The objection raised by Opponent II in point 124 of the Statement of Grounds no longer applies, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims should not be construed as product *per se* claims. Independent Claim 3 as granted corresponds to Claims 3 and 34-40 of Auxiliary Request 1.

9.108 There is no disclosure in D15 of any of the specific therapeutic uses recited in the independent "2nd medical use" Claims 3 or 34-40 of Auxiliary Request 1. Thus, independent Claims 3 and 34-40, and all claims dependent thereon, are novel over D15.

Novelty over Master reference D16 (referred to by Opponent II as D9)

Claims 3-16 and 22-24 as granted

9.109 The objection raised by Opponent II in point 129 of the Statement of Grounds no longer applies, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims should not be construed as product *per se* claims.

Claim 3 as granted

9.110 In point 130 of the Statement of Grounds, Opponent II has alleged that Claim 3 of the Patent as granted lacks novelty in view of D16. The subject-matter of Claim 3 as granted is now to be found in Claims 3 and 34-40 of Auxiliary Request 1.

9.111 Claim 3 of Auxiliary Request 1 is novel over D16, which fails to disclose any of the compounds specifically recited in Claim 3. In this regard, there is no enabling disclosure in D16 of using any antibody that binds specifically to a polypeptide of SEQ ID NO: 59 or 60, as recited in parts e) and f), respectively, of Claim 3.

9.112 D16 also fails to disclose any of the compounds recited in Claims 34-38 or 40 of Auxiliary Request 1, and hence these claims are also novel over D16.

9.113 With regard to Claim 39 of Auxiliary Request 1, this claim is also novel over D16, which fails to explicitly disclose the sequence of SEQ ID NO: 18. In this regard, the D16 ligand sequence illustrated in Figure 1A is 285 amino acids long, whereas SEQ ID NO: 18 of the Patent is only 264 amino acids long (corresponding to amino acid residues 22-285 of the D16 sequence). Furthermore, there is no enabling disclosure in D16 of any antibody that would bind specifically to SEQ ID NO: 18 of the Patent, and Opponent II is incorrect to assume that antibodies raised against the D16 sequence would bind specifically to the short ligand sequence SEQ ID NO: 18. Thus, Claim 39 is novel over D16.

Furthermore, D16 is a merely academic publication, which fails to disclose any of the specific medical conditions recited in Claim 45. Hence, Claim 45 is novel over D16.

Claims 4-12 as granted

9.114 In point 131 of the Statement of Grounds, Opponent II has alleged that "fusion protein" Claims 4-12 of the Patent as granted - insofar as the fusions contain the ztnf4 fragment SEQ ID NO: 18 - lack novelty in view of D16. The subject-matter of Claims 4-12 as granted is now to be found in Claims 4-12 and 41-52 of Auxiliary Request 1.

9.115 None of Claims 4-12 or 41-52 of Auxiliary Request 1 recites a fusion protein in which the first portion comprises the ztnf4 fragment SEQ ID NO: 18. Furthermore, all of the claimed fusions comprise polypeptides containing a BR43x2, TACI or BCMA amino acid sequence. None of these sequences are disclosed in D16, and hence Claims 4-12 and 41-52 of Auxiliary Request 1 are novel over D16.

Novelty over Master reference D17 (referred to by Opponent II as D10)

Claims 3-16 and 22-24 as granted

9.116 The objection raised by Opponent II in point 135 of the Statement of Grounds no longer applies, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims should not be construed as product *per se* claims.

Claim 3 as granted

9.117 In point 136 of the Statement of Grounds, Opponent II has alleged that Claim 3 of the Patent as granted lacks novelty in view of D17. The subject-matter of Claim 3 as granted is now to be found in Claims 3 and 34-40 of Auxiliary Request 1.

9.118 Claim 3 of Auxiliary Request 1 is novel over D17, which fails to disclose any of the compounds specifically recited in Claim 3. In this regard, there is no enabling disclosure in D17 of using any antibody that binds specifically to a polypeptide of SEQ ID NO: 59 or 60, as recited in parts e) and f), respectively, of Claim 3.

9.119 D17 also fails to disclose any of the compounds recited in Claims 34-38 or 40 of

Auxiliary Request 1, and hence these claims are also novel over D17.

9.120 With regard to Claim 39 of Auxiliary Request 1, this claim is also novel over D17, which fails to explicitly disclose the sequence of SEQ ID NO: 18. In this regard, D17 merely refers to the sequence provided by D16. As discussed above, the D16 ligand sequence is 285 amino acids long, whereas SEQ ID NO: 18 of the Patent is only 264 amino acids long (corresponding to amino acid residues 22-285 of the D16 sequence). Also as discussed above, there is no enabling disclosure in D16 (or in D17) of any antibody that would bind specifically to SEQ ID NO: 18 of the Patent. In this regard, the antigen used in D16 and D17 is distinct from (longer than) SEQ ID NO: 18, and hence the D16/ D17 antibodies would not specifically bind to a polypeptide of SEQ ID NO: 18. Hence, Opponent II is incorrect to assume that antibodies raised against the D16 sequence would bind specifically to the short ligand sequence SEQ ID NO: 18. Thus, Claim 39 is novel over D17.

9.121 Furthermore, D17 is another merely academic publication, which fails to disclose any of the specific medical conditions recited in Claim 39. Hence, Claim 39 is novel over D17.

Claims 4-12 as granted

9.122 In point 137 of the Statement of Grounds, Opponent II has alleged that "fusion protein" Claims 4-12 of the Patent as granted - insofar as the fusions contain the ztnf4 fragment SEQ ID NO: 18 - lack novelty in view of D17. The subject-matter of Claims 4-12 as granted is now to be found in Claims 4-12 and 41-52 of Auxiliary Request 1.

9.123 None of Claims 4-12 or 41-52 of Auxiliary Request 1 recites a fusion protein in which the first portion comprises the ztnf4 fragment SEQ ID NO: 18. Furthermore, all of the claimed fusions comprise polypeptides containing a BR43x2, TACI or BCMA amino acid sequence. None of these sequences are disclosed in D17, and hence Claims 4-12 and 41-52 of Auxiliary Request 1 are novel over D17.

Claim 17 as granted

9.124 In point 138 of the Statement of Grounds, Opponent II has alleged that Claim 17 of the Patent as granted lacks novelty in view of D17. Claim 17 as granted corresponds to Claims 1, 3 and 32 of Auxiliary Request 1.

9.125 Claims 1 and 3 are novel over D17, which fails to disclose the compounds recited for use in these claims. Likewise, Claim 32 is novel over D17 since D17 fails to disclose amino acid residues 1-166 of SEQ ID NO: 6.

Claim 18 as granted

9.126 In point 139 of the Statement of Grounds, Opponent II has alleged that Claim 18 of the Patent as granted - to the extent that it relates to systemic lupus erythematosis or rheumatoid arthritis - lacks novelty over D17. The "systemic lupus erythematosis" and "rheumatoid arthritis" aspects of Claim 18 as granted are now found in Claims 13 and 53 of Auxiliary Request 1.

9.127 Claim 13 of Auxiliary Request 1 is dependent (ultimately) on either of Claims 1 or 3, which as discussed above are novel over D17 by virtue of the recited compounds. Thus, Claim 13 is novel over D17 by dependency. Likewise, Claim 53 depends (ultimately) on Claim 32, which is also novel over D17 by virtue of the recited compounds. Thus, Claim 53 is also novel over D17 by dependency.

Claim 20 as granted

9.128 In point 140 of the Statement of Grounds, Opponent II has alleged that Claim 20 of the Patent as granted - to the extent that it relates to nephritis- lacks novelty over D17. The "nephritis" aspect of Claim 20 as granted is now to be found in Claims 14, 27, 29-30, 34, 38-40 and 55 of Auxiliary Request 1.

9.129 Claim 14 of Auxiliary Request 1 is dependent on either of Claims 1 or 3, which are novel over D17 as discussed above by virtue of the recited compounds. Hence, Claim 14 is also novel, by dependency. Claims 27, 29-30, 34, 38 and 40 are novel over D17, which fails to disclose the specific compounds recited for use in these claims. Claim 55 of Auxiliary Request 1 is dependent on any of Claims 28, 31, 35 or

38-39, which are also novel over D17 since none of the compounds recited in these claims are disclosed in D17. Furthermore, with regard to Claim 39, there is no disclosure in D17 of using an antibody or antibody fragment that specifically binds to SEQ ID NO: 18 for manufacture of a medicament for treating any kind of renal disease, such as nephritis. Hence, Claim 39 and dependent Claim 55 are novel over D17.

Novelty over Master reference D18 (referred to by Opponent II as D11)

Claims 3-16 and 22-24 as granted

9.130 The objection raised by Opponent II in point 144 of the Statement of Grounds no longer applies, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims should not be construed as product *per se* claims.

Claim 3 as granted

9.131 In point 145 of the Statement of Grounds, Opponent II has alleged that Claim 3 of the Patent as granted lacks novelty in view of D18. The subject-matter of Claim 3 as granted is now to be found in Claims 3 and 34-40 of Auxiliary Request 1.

9.132 Claim 3 of Auxiliary Request 1 is novel over D18, which fails to disclose any of the compounds specifically recited in Claim 3. In this regard, there is no enabling disclosure in D18 of using any antibody that binds specifically to a polypeptide of SEQ ID NO: 59 or 60, as recited in parts e) and f), respectively, of Claim 3.

9.133 D18 also fails to disclose any of the compounds recited in Claims 34-38 or 40 of Auxiliary Request 1, and hence these claims are also novel over D18.

9.134 With regard to Claim 39 of Auxiliary Request 1, this claim is also novel over D18, which fails to explicitly disclose the sequence of SEQ ID NO: 18. In this regard, the ligand sequence provided in Figure 1 of D18 is 285 amino acids long, whereas SEQ ID NO: 18 of the Patent is only 264 amino acids long (corresponding to amino acid

residues 22-285 of the D18 sequence). Also as discussed above, there is no enabling disclosure in D18 of any antibody that would bind specifically to SEQ ID NO: 18 of the Patent. In this regard, the antigen used in D18 is distinct from (longer than) the antigen SEQ ID NO: 18. Hence, Opponent II is incorrect to assume that antibodies raised against the D18 sequence would bind specifically to the short ligand sequence SEQ ID NO: 18. In this regard, a skilled person would be able to identity a "specifically binding" antibody as a matter of routine, for example by Scatchard analysis (see paragraph 0073 of the Patent specification as granted). Thus, Claim 39 is novel over D18.

Furthermore, D18 fails to disclose any of the specific medical conditions recited in Claim 45. Hence, Claim 45 is novel over D18.

Claims 4-12 as granted

9.135 In point 146 of the Statement of Grounds, Opponent II has alleged that "fusion protein" Claims 4-12 of the Patent as granted - insofar as the fusions contain the ztnf4 fragment SEQ ID NO: 18 - lack novelty in view of D18. The subject-matter of Claims 4-12 as granted is now to be found in Claims 4-12 and 41-52 of Auxiliary Request 1.

9.136 None of Claims 4-12 or 41-52 of Auxiliary Request 1 recite a fusion protein in which the first portion comprises the ztnf4 fragment SEQ ID NO: 18. Furthermore, all of the claimed fusions comprise polypeptides containing a BR43x2, TACI or BCMA amino acid sequence. None of these sequences are disclosed in D18, and hence Claims 4-12 and 41-52 of Auxiliary Request 1 are novel over D18.

Claims 13-15 as granted

9.137 In point 147 of the Statement of Grounds, Opponent II has alleged that Claims 13-15 of the Patent as granted lack novelty in view of D18. The subject-matter of Claims 13-15 is absent from Auxiliary Request 1.

Claims 16 and 17 as granted

9.138 In point 148 of the Statement of Grounds, Opponent II has alleged that Claims 16-17 of the Patent as granted lack novelty in view of D18. Claims 16-17 as granted correspond to Claims 1, 3 and 32 of Auxiliary Request 1, which as discussed above are novel over D18 by virtue of the recited compounds.

Claim 21 as granted

9.139 In point 149 of the Statement of Grounds, Opponent II has alleged that Claim 21 of the Patent as granted - to the extent that it relate to renal neoplasms - lacks novelty in view of D18. The "neoplasms" aspect of Claim 21 as granted has been incorporated into Claims 1, 3, 27-31 and 34-40 of Auxiliary Request 1.

9.140 All of Claims 1, 3, 27-31 and 34-40 of Auxiliary Request 1 are novel over D18, which fails to disclose the compounds recited for use in these claims. Furthermore, the general disclosure in D18 of treating "B cell disorders associated with neoplasia" does not provide an enabling disclosure of treating renal neoplasms, which are a specific type of neoplasm.

Novelty over Master references D19-D24 (referred to by Opponent II as D12-D17)

Claims 1-16 and 22-24 as granted

9.141 The objections raised by Opponent II in point 152 of the Statement of Grounds no longer apply, since, as discussed above, the independent "2nd medical use" claims of Auxiliary Request 1 all recite specific medical conditions to be treated. Thus, these claims should not be construed as product *per se* claims.

Novelty over D19 (priority document of Master reference D2)

9.142 All the claims of Auxiliary Request 1 are novel over D19. In brief, independent Claims 1 and 3 of Auxiliary Request 1 are novel over D19, which relates solely to TACI and fails to recite any of the compounds recited in these claims. In particular, there is no enabling disclosure in D19 of any antibody falling within the scope of parts b-d) of Claims 1 or 3, and Opponent II is incorrect to allege that the anti-TACI antibodies of

D19 would bind specifically to SEQ ID NOs: 2, 4 or 10 of the Patent. In this regard, the present antibodies are raised against specific antigens (namely, a polypeptide of SEQ ID NO: 2, 4 or 10), which are distinct from the TACI antigens used in D19. Hence, the D19 antibodies would not bind specifically to a polypeptide of SEQ ID NO: 2, 4 or 10 (see paragraph 0073 of the Patent specification for a definition of "specifically binding").

9.143 Independent Claims 28-29, 31, 35-36 and 38-39 of Auxiliary Request 1 are also novel over D19, which fails to disclose any of the compounds recited for use in these claims. In this regard, Opponent II is incorrect to allege that D19 discloses a polypeptide of SEQ ID NO: 10, since there is no explicit disclosure of any cysteine-rich domain consensus sequence in D19, let alone the sequence of SEQ ID NO: 10.

9.144 Independent Claims 27, 30, 34, 37 and 40 of Auxiliary Request 1 are novel over D19, which fails to recite any of the specific medical conditions recited in these claims.

9.145 D19 is not citable against independent Claim 32 of Auxiliary Request 1, which is entitled to the 7 January 1999 priority date of the Patent – which precedes the filing date of D19.

9.146 All remaining claims of Auxiliary Request 1 are novel over D19 by dependency.

Novelty over D20 (priority document of Master reference D3)

9.147 All the claims of Auxiliary Request 1 are novel over D20. In brief, independent Claims 1 and 3 of Auxiliary Request 1 are novel over D20, which relates solely to BCMA and fails to disclose any of the compounds recited for use in these claims.

9.148 Independent Claims 27, 29-30, 34, 36-37 and 39-40 of Auxiliary Request 1 are also novel over D20, which fails to disclose any of the compounds recited for use in these claims. In this regard, Opponent II is incorrect to allege that D20 discloses the consensus sequence SEQ ID NO: 10, since there is no explicit disclosure of any Cys-rich consensus sequence in D20, let alone the sequence of SEQ ID NO: 10.

9.149 Independent Claims 28, 31, 35 and 38 of Auxiliary Request 1 are novel over D19, which fails to recite any of the specific medical conditions recited in these claims.

9.150 D20 is not citable against independent Claim 32 of Auxiliary Request 1, which is entitled to the 7 January 1999 priority date of the Patent – which precedes the filing date of D20.

9.151 All remaining claims of Auxiliary Request 1 are novel over D19 by dependency.

Novelty over D21-D24

9.152 All the claims of Auxiliary Request 1 are novel over D21-D24. In brief, independent Claims 1 and 3 of Auxiliary Request 1 are novel over D21-24, which relate solely to ztnf4 and fail to disclose any of the compounds recited for use in these claims.

9.153 Independent Claims 27-31, 34-38 and 40 of Auxiliary Request 1 are also novel over D21-D24, which fail to disclose any of the compounds recited in these claims.

9.154 With regard to Claim 39 of Auxiliary Request 1, this claim is also novel over D21-D24, which all fail to explicitly disclose the sequence of SEQ ID NO: 18. In this regard, the ligand sequences provided in D21-D24 are 285 amino acids long, whereas SEQ ID NO: 18 of the Patent is only 264 amino acids long (corresponding to amino acid residues 22-285 of the D21-D24 sequence). Furthermore, the only antigen used in D21-D24 is the 285 amino acid ligand polypeptide, which is distinct from (longer than) SEQ ID NO: 18 of the present invention and would also present a different antigenic conformation as compared to SEQ ID NO: 18. Thus, the D21-D24 antibodies would not specifically bind a polypeptide of SEQ ID NO: 18. In this regard, it would be a matter of routine for a skilled person to identify whether or not an antibody is "specifically binding", by assessment of the binding affinity (see paragraph 0073 of the Patent as granted). Thus, Claim 39 is novel over D21-D24.

9.155 D21-D24 are not citable against independent Claim 32 of Auxiliary Request 1, which is entitled to the 7 January 1999 priority date of the Patent – which precedes the filing dates of D21-D24.

9.156 All remaining claims of Auxiliary Request 1 are novel over D21-D24 by dependency.

INVENTIVE STEP – ARTICLE 56 EPC AND ARTICLE 100a EPC

BR43x2 aspects of all claims as granted

9.157 In points 157-160 of the Statement of Grounds, Opponent II has alleged that all the claims of the Patent as granted – insofar as they relate to BR43x2 – lack an inventive step in view of Master reference D1. In more detail, Opponent II has alleged that BR43x2, and the use thereof, is obvious over TACI. BR43x2 aspects of the present invention are found in Claims 1, 3 and 24 of Auxiliary Request 1.

9.158 As discussed above, D1 fails to suggest any of the BR43x2 aspects of the present invention. BR43x2 is a non-obvious isoform of TACI since it lacks the highly conserved first cysteine rich domain of TACI. Surprisingly, however, the present inventors have identified that polypeptides comprising the extracellular domain of SEQ ID NO: 2 (ie. SEQ ID NO: 4), and antibodies thereto are therapeutically useful. Thus, Claims 1, 3 and 24 of Auxiliary Request 1 Claim 24 are not obvious over D1.

9.159 Furthermore, the specific mode of action of the compounds recited in Claims 1 and 3 of Auxiliary Request 1 is not suggested by D1. In particular, there is no suggestion in D1 of ztnf4, and hence it would not be obvious to a skilled person that a BR43x2 polypeptide (or antibody thereto) could be used to treat any medical conditions by inhibiting ztnf4 activity or by inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagements. Thus, the BR43x2 aspects as recited in Auxiliary Request 1 have an inventive step over D1.

BCMA aspects of Claims 1-28 and 36-38 as granted

9.160 In point 161 of the Statement of Grounds, Opponent II has alleged that SEQ ID NO: 10, anti-BCMA antibodies, BCMA fusion proteins, and the currently claimed uses thereof all lack an inventive step in view of Master references D11-D13 (referred to by Opponent II as D3, D5 and D4, respectively).

9.161 As discussed above, the sequence of SEQ ID NO: 10, and antibodies that specifically bind to a polypeptide of SEQ ID NO: 10, are inventive over the cited prior art. Neither D11 nor D13 provides any suggestion of SEQ ID NO: 10, and D12 - which identifies the cysteine rich domain of BCMA - fails to suggest any therapeutic use for this sequence. In view of D11-D13, it would not be obvious that a polypeptide of SEQ ID NO: 10, or a specifically binding antibody raised against this polypeptide, could be used to inhibit ztnf4 activity or engagements, or to treat the specific medical conditions recited in the Auxiliary Request 1 claims. Thus, the SEQ ID NO: 10 aspects of Auxiliary Request 1 are inventive over D11-D13.

9.162 Antibodies that specifically bind to a polypeptide of SEQ ID NO: 8 are not obvious in view of the D11-D13 antibodies, which were raised against an N-terminally truncated BCMA-GST fusion protein. There is no suggestion in any of D11-D13 of raising an antibody against full-length SEQ ID NO: 8, and hence these antibodies are not obvious over D11-D13.

9.163 With regard to fusion proteins containing a BCMA sequence (Claims 5, 42-43 and 45 of Auxiliary Request 1) these claims are also inventive over D11-D13, which fail to suggest these specific fusions, or the therapeutic uses thereof.

9.164 In this regard, the presently claimed therapeutic applications of BCMA (and antibodies/ fusions) would not have been obvious in view of D11-D13. These citations are all academic in nature, and do not suggest any therapeutic uses, let alone treatment of the specific medical conditions recited in the "use" claims of Auxiliary Request 1. In this regard, any vague references in D11-D13 to expression in B cell lines would not suggest any specific therapies to a skilled person.

9.165 Furthermore, there is no suggestion in D11-D13 that any of these BCMA-related compounds could be used to inhibit the activity of ztnf4 or to inhibit engagements of ztnf4 with the BR43x2, TACI or BCMA receptors. Indeed, none of D11-D13 even suggests a ligand for BCMA. Thus, the BCMA aspects of Auxiliary Request 1 are also all inventive over D11-D13.

Ztnf4 aspects of Claims 3-28 as granted

9.166 In point 162 of the Statement of Grounds, Opponent II has alleged that Claims 3-38 of the Patent as granted - to the extent to which they relate to antibodies that specifically binds to ztnf4 (SEQ ID NO: 18) – lack an inventive step in view of Master references D5, D6 and D15 (referred to by Opponent II as D6-D8). In this regard, the only claim of Auxiliary Request 1 that relates to this subject-matter is Claim 39.

9.167 Neither D6 nor D15 provide any suggestion of the sequence SEQ ID NO: 18, and hence the recited antibody would not be obvious in view of these documents. With regard to D5, there is no suggestion of any of the specific medical uses of anti-SEQ ID NO: 18 antibodies recited in Claim 39. In this regard, alleged references in D5 to treating "autoimmune diseases" in general would not make it obvious to treat the specific autoimmune conditions myasthenia gravis and Crohn's Disease. Thus, Claim 39 is inventive over D5, D6 and D15.

Inventive Step in view of Master references D16, D17 and D18

9.168 In point 164 of the Statement of Grounds, Opponent II has alleged that Master references D16-D18 (referred to as D9-D11 by Opponent II) are relevant to inventive step of all claims to the extent to which they are not entitled to the 7 January 1999 priority date. D16-D18 all relate to ztnf4, but none of these documents suggests the 264 amino acid sequence of SEQ ID NO: 18.

9.169 None of D16-D18 identifies the specific receptor for the ztnf4 ligand. In particular, there is no disclosure in D16-D18 that ztnf4 might act through/ engage with BR43x2, TACI or BCMA. Thus, it would not have been obvious from any of D16-D18 that the compounds recited in the "use" claims of Auxiliary Request 1 could be used to inhibit ztnf4 activity or receptor-ztnf4 engagements. Hence, all the "use" claims of Auxiliary Request 1 are inventive over D16-D18.

9.170 Furthermore, D16-D18 are all academic publications, relating to characterization of ztnf4, and they do not suggest any therapeutic use for ztnf4. In particular, it would not be obvious from D16-D18 that a specifically binding anti-SEQ ID NO: 18 antibody

could be used to treat the specific medical conditions recited in Claim 39 of Auxiliary Request 1. Hence, this claim is inventive over D16-D18.

SUFFICIENCY OF DISCLOSURE – ARTICLE 83 EPC AND ARTICLE 100b EPC

Claims 13-15 as granted

9.171 In point 166 of the Statement of Grounds, Opponent II has alleged that the subject-matter of Claims 13-15 of the Patent as granted - concerning the treatment of B lymphocytes - is insufficiently disclosed.

9.172 The subject-matter of Claims 13-15 as granted is absent from Auxiliary Request 1, and hence Opponent II's objection does not apply to Auxiliary Request 1.

Antibodies or antibody fragments that bind specifically to SEQ ID NOs: 18 and 20.

9.173 In point 167 of the Statement of Grounds, Opponent II has alleged that Claim 3 lacks sufficient disclosure to the extent to which it relates to antibodies or antibody fragments that bind specifically to SEQ ID NOs: 18 and 20.

9.170 Opponent II is incorrect to take this view since the polypeptide sequences of SEQ ID NOs: 18 and 20 are provided in the Patent specification. A skilled person would consider it routine to raise antibodies against these sequences. Furthermore, a skilled person would determine as a matter of routine whether or not an antibody is "specifically binding" by determining the binding affinity (eg. by Scatchard analysis – see paragraph 0073 of the Patent specification).

9.171 Thus, antibodies or antibody fragments that bind specifically to SEQ ID NOs: 18 and 20 are sufficiently disclosed in the Patent specification as filed.

10 OBSERVATIONS IN REPLY TO OPPONENT III

ADDED MATTER – ARTICLE 123(2) EPC AND ARTICLE 100c EPC

Claims 1b) and 3b) as granted

10.1 On page 5 of the Statement of Grounds, Opponent III has alleged that Claims 1b) and 3b) contain subject-matter that extends beyond the content of the application as filed. In more detail, Opponent III has alleged that there is no basis in the application as filed for a "soluble" polypeptide comprising the extracellular domain of TACI. Claims 1b) and 3b) of the Patent as granted correspond to Claims 27 and 34 of Auxiliary Request 1.

10.2 Opponent III is incorrect to take this view, since the PCT application as filed discloses soluble polypeptides that comprise the TACI extracellular domain. In this regard, we would refer the Opposition Division to page 13, lines 18-32 of the PCT application as filed, which described soluble receptors. Hence, it is evident that soluble versions of the TACI receptor are envisaged by the PCT application as filed. Furthermore, reference to soluble TACI polypeptides is found throughout the PCT specification as filed – for example on page 46, line 20; page 54, lines 19-20; page 57, lines 12 and 33; page 61, lines 15-20; page 63, line 31; page 64, line 21; page 83, line 6; and page 84, lines 25-28 of the PCT application as filed. In addition, Examples 10 and 11 of the PCT publication both illustrate the use of soluble polypeptides comprising the TACI extracellular domain.

10.3 Thus, the subject-matter of Claims 1b) and 3b) as granted is disclosed in the PCT application as filed, and no matter has been added beyond the content of the application as filed.

Claim 36 as granted

10.4 Also on page 5 of the Statement of Grounds, Opponent III has alleged that Claim 36 as granted - relating to pharmaceutical compositions of specifically binding antibodies - is an unsupported generalization of the disclosure of the application as filed, and

thus allegedly contravenes Article 123(2) EPC. Claim 36 as granted corresponds to Claim 24 of Auxiliary Request 1.

10.5 Opponent III is incorrect to take the view that compositions comprising an antibody *per se* are not disclosed in the PCT specification as filed. In this regard, we would draw the Opposition Division's attention to line 23 on page 64 of the PCT specification, which recites that "the invention also provides antibodies". There is no functional limitation associated with this sentence. Thus, compositions comprising an antibody *per se* have basis in the PCT specification as filed.

NOVELTY – ARTICLE 54 EPC AND ARTICLE 100a EPC

Novelty over Master reference D1

Claims 1 and 3 as granted

10.6 D1 fails to disclose the specific medical conditions recited in Claims 27, 30, 34 and 37 of Auxiliary Request 1. In this regard, none of the passages recited by Opponent III from D1 on page 12 of the Statement of Grounds provides a disclosure of any of the specific therapeutic uses recited in these claims. Thus, Claims 27, 30, 34 and 37 of Auxiliary Request 1 are novel over D1.

10.7 At the top of page 12 of the Statement of Grounds, Opponent III has alleged that amino acid residues 1-166 of SEQ ID NO: 6 are disclosed in D1, and that Claim 1 (part l) and Claim 3 (part m) of the Patent as granted lack novelty over D1. Claims 1l and 3m correspond to Claims 32 and 40 of Auxiliary Request 1.

10.8 Claims 32 and 40 are novel with respect to D1, which does not disclose the mechanism of action of amino acid residues 1-166 of SEQ ID NO: 6. In more detail, there is no disclosure of any specific ligand for TACI in D1, let alone ztnf4. In particular, there is no disclosure in D1 of inhibiting the activity of ztnf4. Furthermore, D1 fails to disclose using amino acid residues 1-166 of SEQ ID NO: 6 for the manufacture of a medicament for treating any medical condition by inhibiting ztnf4 activity – let alone the specific medical conditions recited in Claim 32. Thus, Claim 32

is novel over D1. Likewise, there is no disclosure in D1 of inhibiting engagement of ztnf4 with the BR43x2, TACI, or BCMA receptor, and D1 fails to disclose using amino acid residues 1-166 of SEQ ID NO: 6 for the manufacture of a medicament for treating any medical condition by inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement. Thus, Claim 40 is novel over D1.

10.9 In the 2nd paragraph of page 12 of the Statement of Grounds, Opponent III has alleged that the sequence of SEQ ID NO: 10 is disclosed in D1, and that Claim 1d) and Claims 3d) of the Patent as granted lacks novelty over D1. Claims 1d) and 3d) correspond to Claims 29 and 36 of Auxiliary Request 1.

10.10 Opponent III is incorrect to allege that D1 discloses the sequence of the consensus polypeptide SEQ ID NO: 10 of the Patent, and Claims 29 and 36 of Auxiliary Request 1 are therefore novel over D1. In more detail, the "Prosite" consensus sequence provided in D1 (page 19, lines 20-25) is more flexible than (ie. broader than) SEQ ID NO: 10. Since SEQ ID NO: 10 of the Patent is more specific than the sequence provided by D1, SEQ ID NO: 10 is novel over D1. Furthermore, D1 fails to recite the specific medical conditions recited in these claims, and hence Claims 29 and 36 are novel over D1.

Claims 13-27 as granted

10.11 In the 4th paragraph of page 12 of the Statement of Grounds, Opponent III has alleged that all of Claims 13-27 of the Patent as granted lack novelty over D1. The subject-matter of Claims 13-15 and 23 as granted is absent from Auxiliary Request 1. The subject-matter of Claims 16-22 and 24-27 as granted has been incorporated into Claims 1, 3, 13-15, 27-32, 34-40 and 53-55 of Auxiliary Request 1.

10.12 D1 relates solely to TACI and does not disclose any of the specific compounds recited in Claims 1 and 3. In more detail, there is no disclosure in D1 of any antibody that would bind specifically to the polypeptides SEQ ID NO: 2, 4 or 10. Furthermore, D1 does not disclose ztnf4, let alone inhibition of ztnf4 activity or inhibiting of BR43x2, TACI or BCMA receptor-ztnf4 engagement using a medicament made using the recited compounds. Thus, Claims 1 and 3 of Auxiliary Request 1 are novel over D1.

Claims 13-15 are dependent on any of Claims 1 or 3, and are thus novel by dependency.

10.13 With regard to Claims 28-29, 31, 35-36 and 38, D1 does not disclose any of the compounds recited in these claims, and hence these claims are novel over D1.

10.14 With regard to Claims 27, 30, 32, 34, 37 and 40, as discussed above, these claims are also novel over D1, which does not recite the mechanism of action of the claimed compounds, or the specific therapeutic uses recited in these claims.

10.15 Claims 53-55 are all novel by virtue of dependency on claims selected from Claims 28, 31-32, 35 or 38, which are all novel over D1 as discussed above.

Claim 2 as granted

10.16 In the 5th paragraph of page 12 of the Statement of Grounds, Opponent III has alleged that the subject-matter of Claim 2 of the Patent as granted lacks novelty over D1. Claim 2 as granted corresponds to Claims 2 and 33 of Auxiliary Request 1.

10.17 Claim 2 of Auxiliary Request 1 depends on Claim 1, which is novel over D1 as discussed above by virtue of the recited compounds. Claim 33 of Auxiliary Request 1 depends on any of Claims 27-32, which are novel over D1 as discussed above, by virtue of the specific medical conditions (Claims 27, 30 and 34), the recited compounds (Claims 28-29 and 31) and the specific mechanism of action (Claim 32). Thus, Claims 2 and 33 are also novel over D1, by virtue of their dependency.

Claims 4-6 and 8 as granted

10.18 In the 6th to 8th paragraphs of page 12 of the Statement of Grounds, Opponent III has alleged that the subject-matter of Claims 4-6 and 8 of the Patent as granted is disclosed in D1, and hence has alleged that these claims lack novelty over D1. Claims 4-6 and 8 as granted correspond to Claims 4-6, 8, 41-45 and 48 of Auxiliary Request 1.

10.19 Claims 4-6 of Auxiliary Request 1 are dependent on either of Claims 1 and 3, which are novel over D1, by virtue of the recited compounds. Furthermore, the fusion protein of Claim 4 must comprise amino acid residues 25-58 of SEQ ID NO: 2. There is no disclosure in D1 of SEQ ID NO: 2, of amino acid residues 25-58 of SEQ ID NO: 2 or of any fusion protein comprising this amino acid sequence. With regard to dependent Claim 5b) of Auxiliary Request 1, the polypeptide sequence consisting of amino acid residues 105-166 of SEQ ID NO: 6 must be present in the first portion further to (ie. in addition to) the sequences of Claim 4, on which Claim 5 depends. Thus, Claims 4-6 of Auxiliary Request 1 are novel over D1.

10.20 With regard to Claims 41-45 and 48 of Auxiliary Request 1, the independent base claims (selected from Claims 27-29, 32, 34-36 and 40) on which these claims depend are novel over D1, by virtue of the specific medical conditions/ recited compounds/ or mechanism of action. Thus, Claims 41-45 and 48 are novel by virtue of dependency. With particular regard to Claim 41, there is no disclosure in D1 of any fusion protein comprising the specific amino acid sequences of SEQ ID NO: 6 recited in parts a-c) of Claim 41. Thus, Claims 41-45 of Auxiliary Request 1 are also novel over D1.

10.21 Claims 8 and 48 of Auxiliary Request 1 are dependent on novel Claims 4-7 and 41-45, respectively, and hence are also novel over D1 by virtue of dependency.

Claims 36-38 as granted

10.22 In the 9th paragraph of page 12 of the Statement of Grounds, Opponent III has alleged that the subject-matter of Claims 36-38 - insofar as Claim 36 relates to an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 6 – lack novelty over D1. Claims 36-38 as granted correspond to Claims 24-26 of Auxiliary Request 1.

10.23 Opponent III's objections with regard to these pharmaceutical composition claims no longer apply, since Claims 24-26 of Auxiliary Request 1 do not recite any anti-TACI antibodies. Furthermore, there is no disclosure in D1 of any antibody or antibody fragment that binds specifically to any of SEQ ID NOs: 2, 4, or 10. Thus, Claims 24-26 of Auxiliary Request 1 are novel over D1.

Novelty over Master reference D2

Claim 1g) and 3g) as granted

10.24 At the top of page 13 of the Statement of Grounds, Opponent III has alleged that part g) of Claims 1 and 3 of the Patent as granted lacks novelty in view of D2. Claims 1g) and 3g) as granted correspond to Claims 30 and 37 of Auxiliary Request 1.

10.25 Claims 30 and 37 of Auxiliary Request 1 are novel over D2, which fails to recite treating any of the specific medical conditions recited therein. In this regard, asthma, bronchitis and emphysema are distinct conditions from acute respiratory distress syndrome (allegedly described in D2); renal neoplasms are a specific type of cancer, which are not disclosed by the vague, general reference in D2 to treating tumours; Crohn's Disease is a specific autoimmune disease, distinct from other autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and diabetes (allegedly described in D2); and there is no enabling disclosure in D2 of treating specific types of inflammation that are associated with joint pain, swelling or septic shock.

Claims 16-18 and 22-27 as granted

10.26 In the 2nd paragraph if page 13 of their Statement of Grounds, Opponent III has alleged that the therapeutic uses recited in Claims 16-18 and 22-27 of the Patent as granted are known from D2, and that these claims lack novelty over D2. The subject-matter of Claim 23 is not present in Auxiliary Request 1. The subject-matter of Claims 16-18, 22 and 24-27 as granted has been incorporated into Claims 1, 3, 13, 15, 27-32, 34-40 and 53-55 of Auxiliary Request 1.

10.27 Claims 1 and 3 of Auxiliary Request 1 are novel over D2, which relates only to TACI and fails to disclose any of the specific compounds recited in these claims. In particular, there is no enabling disclosure in D2 of any antibody that binds specifically to a polypeptide of SEQ ID NO: 2, 4 or 10. Thus, Claims 1 and 3 are novel, and Claims 13 and 15, which depend on either of Claims 1 or 3, are novel by dependency.

10.28 Independent Claims 28-29, 31, 35-36 and 38 are all novel over D2, which fails to recite any of the compounds recited for use in these claims.

10.29 With regard to independent Claims 27, 30, 34, 37, and 40 of Auxiliary Request 1, there is no disclosure in D2 of any of the specific medical conditions recited in these claims, (see above with regard to Claims 30 and 37, for example). Hence, Claims 27, 30, 34, 37, and 40 of Auxiliary request are novel over D2.

10.30 With regard to Claim 32, this claim is entitled to the 7 January 1999 priority date of the Patent, which precedes the priority date of D2. Hence, D2 is not citable against this claim for novelty considerations.

10.31 Claims 53-55 of Auxiliary Request 1 are also novel over D2, by virtue of dependency.

Claim 36 as granted

10.32 In the 4th paragraph of page 13 of the Statement of Grounds, Opponent III has alleged that Claim 36 of the Patent as granted – to the extent that it relates to an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 6 – lacks novelty over D2. Claim 36 as granted corresponds to Claim 24 of Auxiliary Request 1.

10.33 Opponent III's objections with regard to this pharmaceutical composition claim no longer applies, since Claim 24 of Auxiliary Request 1 does not recite any anti-TACI antibodies. Furthermore, there is no disclosure in D1 of any antibody or antibody fragment that binds specifically to any of SEQ ID NOs: 2, 4, or 10, as recited in Claim 24 of Auxiliary Request 1. Thus, Claim 24 of Auxiliary Request 1 is novel over D1.

Novelty over Master reference D3

Claims 1 and 3, parts c), d) and h), as granted

10.34 At the top of page 14 of the Statement of Grounds, Opponent III has alleged that D3 discloses the compounds recited in parts c), d) and h) of Claims 1 and 3 of the Patent

as granted, and that these claims therefore lack novelty over D3. Parts c), d) and h) of Claims 1 and 3 as granted correspond to Claims 28-29, 31, 35-36 and 38 of Auxiliary Request 1.

10.35 D3 fails to disclose any of the specific medical conditions to be treated according to Claims 28-29, 31, 35-36 and 38 of Auxiliary Request 1. In more detail, none of the passages from D3 quoted by Opponent III provides an enabling disclosure of any of the specific medical conditions recited in these claims.

10.36 In this regard, treatment of the specific conditions systemic lupus erythematosis, myasthenia gravis, multiple sclerosis and rheumatoid arthritis is not disclosed by the alleged general teaching in D3 of treating "autoimmune diseases". Likewise, treatment of end stage renal failure is not disclosed by the alleged generic disclosure in D3 of treating unspecified "renal disorders". Renal neoplasms and multiple myelomas are specific types of cancers, and are not unambiguously disclosed by an alleged reference in D3 to "cancer". Furthermore, there is no enabling disclosure in D3 of treating specific types of inflammation associated with joint pain, swelling, anaemia or septic shock. The remaining therapeutic uses recited in Claims 28-29, 31, 35-36 and 38 of Auxiliary Request 1 are also not disclosed in D3.

10.37 Thus, Claims 28-29, 31, 35-36 and 38 of Auxiliary Request 1 are all novel over D3.

Claims 13, 16-17, 22-25 and 27 as granted

10.38 Towards the bottom of page 14 of the Statement of grounds, Opponent III has raised a number of specific novelty allegations with regard to the therapeutic uses recited in Claims 13, 16-17, 22-25 and 27 of the Patent as granted (to the extent to which they depend on parts c), d) or h) of Claims 1 or 3). The subject-matter of Claims 13 and 23 is absent from Auxiliary Request 1. The subject-matter of Claims 16-17, 22, 24-25 and 27 as granted, when dependent on parts c), d) or h) of Claims 1 or 3, is incorporated into Claims 28, 29, 31, 35, 36, 38 and 55 of Auxiliary Request 1.

10.39 As discussed above, independent Claims 28, 29, 31, 35, 36 and 38 of Auxiliary Request 1 are all novel over D3, which does not disclose the recited specific medical

conditions. As discussed above, systemic lupus erythematosis, myasthenia gravis, multiple sclerosis and rheumatoid arthritis are specific medical conditions that are not unambiguously disclosed by the alleged general teaching in D3 of treating unspecified "autoimmune diseases". There is also no enabling disclosure in D3 of inhibiting effector T cells, let alone effecting immunosuppression thereby. Furthermore, the alleged generic disclosure in D3 of treating inflammation does not provide any disclosure of treating specific types of inflammation associated with joint pain, swelling, anaemia or septic shock, as recited in Claims 34, 35, 37, 41, 42 and 44 of Auxiliary Request 1. Thus, these claims are all novel over D3.

10.40 Dependent Claim 55 of Auxiliary Request 1 is novel over D3 by virtue of their dependency on any of novel Claims 28, 31, 35 or 38-39.

Claims 4-6 and 8-9 as granted

10.41 In the 2nd paragraph from the bottom of page 14 of the Statement of Grounds, Opponent III has alleged that fusion protein Claims 4-6 and 8-9 of the Patent as granted lack novelty over D3. Claims 4-6 and 8-9 as granted correspond to Claims 4-6, 8-9, 41-45 and 48-49 of Auxiliary Request 1.

10.42 Claims 4-6 and 8-9 of Auxiliary Request 1 depend (ultimately) on Claims 1 or 3, which are both novel over D3, since D3 fails to recite any of the compounds recited in Claim 1 or Claim 3. Thus, Claims 4-6 and 8-9 are novel by dependency. Furthermore, the fusion protein of Claim 4 must comprise amino acid residues 25-58 of SEQ ID NO: 2. There is no disclosure in D3 of SEQ ID NO: 2, of amino acid residues 25-58 of SEQ ID NO: 2 or of any fusion protein comprising this amino acid sequence. With regard to dependent Claim 5c) of Auxiliary Request 1, the polypeptide sequence consisting of amino acid residues 89-150 of SEQ ID NO: 8 must be present in the first portion further to (ie. in addition to) the sequences of Claim 4, on which Claim 5 depends. Thus, Claims 4-6 and 8-9 of Auxiliary Request 1 are novel over D3.

10.43 With regard to Claims 41-45 and 48-49 of Auxiliary Request 1, these claims all depend on novel claims selected from Claims 27-29, 32, 34-36 or 40, and hence are novel by dependency. With particular regard to Claim 42, there is no disclosure in D3

of any fusion protein comprising the specific amino acid sequences of SEQ ID NO: 8 recited in parts a-d) of Claim 42. Thus, independent Claims 41-45 of Auxiliary Request 1, and their dependent Claims 48-49, are also novel over D3.

Claims 36 and 37 as granted

10.44 In the last paragraph on page 14 of the Statement of Grounds, Opponent III has alleged that Claims 36-37 of the Patent as granted – insofar as they relate to an antibody or antibody fragment that bonds specifically to a polypeptide of SEQ ID NO: 8 - lack novelty in view of D3. Claims 36 and 37 as granted correspond to Claims 24-25 of Auxiliary Request 1.

10.45 Opponent III's objections with regard to these pharmaceutical composition claims no longer apply, since Claims 24-25 of Auxiliary Request 1 do not recite any anti-BCMA antibodies. Furthermore, there is no enabling disclosure in D3 of any antibody or antibody fragment that binds specifically to any of SEQ ID NOs: 2, 4, or 10. Thus, Claims 24-25 of Auxiliary Request 1 are novel over D3.

Novelty over Master reference D4

Claims 1 and 3, parts c) and d), as granted

10.46 In the 5th paragraph of page 15 of the Statement of Grounds, Opponent III has alleged that D4 discloses the compounds recited in parts c) and d) of Claims 1 and 3 of the Patent as granted, and that these claims therefore lack novelty over D3. Parts c) and d) of Claims 1 and 3 as granted correspond to Claims 28, 29, 35 and 36 of Auxiliary Request 1.

10.47 D4 fails to disclose any of the specific medical conditions to be treated according to Claims 28, 29, 35 and 36 of Auxiliary Request 1. In particular, none of the alleged disclosures of D4 quoted by Opponent III provides an enabling disclosure of any of the specific medical conditions recited in these claims.

10.48 In more detail, treatment of the specific conditions systemic lupus erythematosis,

myasthenia gravis, multiple sclerosis and rheumatoid arthritis is not disclosed by the general description in D4 of treating "autoimmune diseases". Likewise, the specific treatment of end stage renal failure is not disclosed by the generic disclosure in D4 of treating unspecified "renal disorders". Renal neoplasms and multiple myelomas are specific types of cancers, and are not unambiguously disclosed by an alleged reference in D4 to "cancer". Furthermore, there is no enabling disclosure in D4 of treating specific types of inflammation associated with joint pain, swelling, anaemia or septic shock. There is also no reference in D4 of treating asthma, bronchitis, emphysema, light chain neuropathy or amyloidosis, or of inhibiting T cells. Thus, Claims 28, 29, 35 and 36 of Auxiliary Request 1 are novel over D4.

Claims 13, 16-17, 22-25 and 27 as granted

10.49 In the 6th paragraph on page 15 of the Statement of Grounds, Opponent III has alleged that the subject-matter of Claims 13, 16-17, 22-25 and 27 of the Patent as granted lack novelty over D4. The subject-matter of Claims 13 and 23 is absent from Auxiliary Request 1. The subject-matter of Claims 16-17, 22, 24-25 and 27 as granted is incorporated into Claims 1, 3, 28, 31-32, 35 and 38 of Auxiliary Request 1.

10.50 There is no disclosure in D4 of any of the compounds recited in Claims 1 or 3 of Auxiliary Request 1, and hence these claims are novel.

10.51 With regard to Claim 32 of Auxiliary Request 1, this Claim is entitled to the 7 January 1999 priority date, which precedes the priority date of D4. Hence, D4 is not citable against Claim 32.

10.52 With regard to Claims 28, 31, 35 and 38 of Auxiliary Request 1, as discussed above, there is no disclosure in D4 of any of the specific medical conditions recited in these claims, and hence Claims 28, 31, 35 and 38 are novel over D4.

Claim 1g) as granted

10.53 In paragraph 7 on page 15 of the Statement of Grounds, Opponent III has alleged that Claims 1g) and 3g) of the Patent as granted lack novelty in view of D4. Claims 1g)

and 3g) as granted correspond to Claims 30 and 37 of Auxiliary Request 1.

10.54 Claims 30 and 37 of Auxiliary Request 1 relate to antibodies or antibody fragments that bind specifically to a polypeptide of SEQ ID NO: 6 – ie. a TACI polypeptide. Since D4 relates solely to BCMA, and fails to disclose TACI, let alone any anti-TACI antibody, these claims are novel over D4.

Claims 36 and 37 as granted

10.55 In paragraph 8 of page 15 of the Statement of Grounds, Opponent III has alleged that Claims 36 and 37 of the Patent as granted – to the extent to which they relate to an antibody or antibody fragment that binds specifically to a polypeptide of SEQ ID NO: 8 – lack novelty over D4. Claims 36 and 37 as granted correspond to Claims 24-25 of Auxiliary Request 1.

10.56 Opponent III's objections with regard to these pharmaceutical composition claims no longer apply, since Claims 24-25 of Auxiliary Request 1 do not recite any anti-BCMA antibodies. Furthermore, D4 does not provide an enabling disclosure of any antibody or antibody fragment that binds specifically to any of SEQ ID NOs: 2, 4, or 10. Thus, Claims 24-25 of Auxiliary Request 1 are novel over D4.

Novelty of Claim 3j) over Master reference D5

10.57 At the top of page 16 of the Statement of Grounds, Opponent III has alleged that Claim 3j) of the Patent as granted lacks novelty over D5. Furthermore, Opponent III has alleged that amendment of Claim 3j) to recite the therapeutic uses recited in Claims 13, 16-19 or 20-27 of the Patent as granted would not restore novelty. Claim 3j) as granted corresponds to Claim 39 of Auxiliary Request 1.

10.58 Claim 39 of Auxiliary Request 1 is novel over D5, which fails to recite the specific medical conditions recited in Claim 39. In this regard, the alleged general disclosure in D5 of treating "autoimmune disease" does not provide an enabling disclosure of treating the specific autoimmune diseases myasthenia gravis and Crohn's disease; and the alleged generic disclosure in D5 of treating inflammatory diseases is not

enabling for treating specific types of inflammation that are associated with joint pain or swelling. Bronchitis and emphysema are distinct medical conditions from asthma, which is allegedly disclosed in D5. The remaining medical conditions recited in Claim 39 are also not disclosed in D5, and hence Claim 39 of Auxiliary Request 1 is novel over D5.

Novelty of Claim 3j) over Master reference D6

10.59 On page 16 of the Statement of Grounds, Opponent III has alleged that Claim 3j) of the Patent as granted lacks novelty over D6. Furthermore, Opponent III has alleged that amendment of Claim 3j) to recite the therapeutic uses recited in Claims 16-18, 22-25 or 27 of the Patent as granted would not restore novelty. Claim 3j) as granted corresponds to Claim 39 of Auxiliary Request 1.

10.60 Claim 39 of Auxiliary Request 1 is novel over D6, which fails to recite the specific anti-SEQ ID NO: 18 antibody used or any of the medical conditions recited in Claim 39. In more detail, D6 fails to disclose any polypeptide having the sequence of SEQ ID NO:18. Whereas the D6 polypeptide is 285 amino acids long, SEQ ID NO: 18 of the Patent is only 264 amino acids long, and represents a specific fragment of the D6 polypeptide sequence from amino acids 22-285. Thus, there is no enabling disclosure in D6 of an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 18, as recited in Claim 39. Furthermore, there is no disclosure in D6 of using such an antibody for manufacture of a medicament for treating a medical condition by inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement. Hence, Claim 39 of Auxiliary Request 1 is novel over D6.

10.61 Moreover, none of the specific medical conditions recited in Claim 39 are disclosed in D6. In this regard, the alleged generic disclosure in D6 of treating "autoimmune disease" does not provide an enabling disclosure of treating the specific autoimmune diseases myasthenia gravis and Crohn's disease; and the alleged general disclosure in D6 of treating inflammation is not enabling for treating specific types of inflammation that are associated with joint pain or swelling. Bronchitis and emphysema are distinct medical conditions from acute respiratory distress syndrome, which is allegedly disclosed in D6. Renal neoplasms are a specific type of cancer,

and are not unambiguously disclosed by an alleged reference in D6 to treating "cancer". None of the other specific medical conditions recited in Claim 39 are disclosed in D6, and hence Claim 39 of Auxiliary Request 1 is novel over D6.

Novelty of Claim 3j) over Master reference D7

10.62 Towards the bottom of page 16 of the Statement of Grounds, Opponent III has alleged that Claim 3j) of the Patent as granted lacks novelty over D7. Furthermore, Opponent III has alleged that amendment of Claim 3j) to recite the therapeutic uses recited in Claims 16-17 or 22-24 of the Patent as granted would not restore novelty. Claim 3j) as granted corresponds to Claim 39 of Auxiliary Request 1.

10.63 D7 fails to recite the specific anti-SEQ ID NO: 18 antibody used or any of the medical conditions recited in Claim 39. In more detail, D7 fails to disclose any polypeptide having the sequence of SEQ ID NO:18. Whereas the D7 polypeptide is 285 amino acids long, SEQ ID NO: 18 of the Patent is only 264 amino acids long, and represents a specific fragment of the D7 polypeptide sequence from amino acids 22-285. In addition, there is no enabling disclosure in D7 of any antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 18, as recited in Claim 39. Furthermore, there is no disclosure in D7 of using such a specifically binding antibody for manufacture of a medicament for treating a medical condition by inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement. Hence, Claim 39 of Auxiliary Request 1 is novel over D7.

10.64 In addition, none of the specific medical conditions recited in Claim 39 are disclosed in D7. In this regard, an alleged reference in D7 to treating "cancers" does not unambiguously disclose treatment of renal neoplasms, which are a specific type of cancer. Furthermore, an alleged vague reference in D7 to ztnf4 having a regulatory role in the immune system does not provide an enabling disclosure of treating the specific autoimmune disorders myasthenia gravis and Crohn's disease. D7 also fails to disclose any of the other conditions recited in Claim 39, and hence Claim 39 of Auxiliary Request 1 is novel over D7.

Novelty of Claim 3j) over Master reference D8

10.65 At the top of page 17 of the Statement of Grounds, Opponent III has alleged that Claim 3j) of the Patent as granted lacks novelty over D8. Furthermore, Opponent III has alleged that amendment of Claim 3j) to recite the therapeutic uses recited in Claims 16-18, 22-25 or 27 of the Patent as granted would not restore novelty. Claim 3j) as granted corresponds to Claim 39 of Auxiliary Request 1.

10.66 D8 fails to recite the specific anti-SEQ ID NO: 18 antibody used in Claim 39 of Auxiliary Request 1, or any of the medical conditions recited in Claim 39 of Auxiliary Request 1. In more detail, whereas the D8 ligand polypeptide is 285 amino acids long, SEQ ID NO: 18 of the Patent is only 264 amino acids long, and represents a specific fragment of the D8 polypeptide sequence from amino acids 22-285. Thus, D8 fails to disclose any polypeptide having the sequence of SEQ ID NO:18. In addition, there is no enabling disclosure in D8 of any antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 18, as recited in Claim 39. Furthermore, there is no disclosure in D8 of using such a specifically binding antibody for manufacture of a medicament for treating a medical condition by inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement. Hence, Claim 39 of Auxiliary Request 1 is novel over D8.

10.67 Furthermore, D8 fails to disclose any of the specific medical conditions recited in Claim 39 of Auxiliary Request 1. In this regard, an alleged reference in D7 to treating unspecified "cancerous conditions" does not unambiguously disclose treatment of renal neoplasms, which are a specific type of cancer. The alleged generic disclosure in D8 of treating "autoimmune disorders" does not provide an enabling disclosure of treating the specific autoimmune disorders myasthenia gravis and Crohn's disease as recited in Claim 39; and the alleged general disclosure in D8 of treating inflammatory responses is not enabling for treating specific types of inflammation that are associated with joint pain or swelling. D8 also fails to disclose any of the other conditions recited in Claim 39, and hence Claim 39 is novel over D8.

Novelty over Master reference D13

Claim 36 as granted

10.68 Towards to bottom of page 17 of the Statement of Grounds, Opponent III has alleged that Claim 36 of the Patent as granted lacks novelty over D13, to the extent that Claim 36 relates to an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 8 (ie. Claim 36d)). Claim 36 as granted corresponds to Claim 24 of Auxiliary Request 1.

10.69 Opponent III's objections with regard to these pharmaceutical composition claims no longer apply, since Claim 24 of Auxiliary Request 1 does not recite any anti-BCMA antibodies. Furthermore, D13 does not provide an enabling disclosure of any antibody or antibody fragment that binds specifically to any of SEQ ID NOs: 2, 4, or 10. Thus, Claims 24-26 of Auxiliary Request 1 are novel over D13.

INVENTIVE STEP – ARTICLE 56 EPC AND ARTICLE 100a EPC

Claims 1 and 3 as granted

10.70 On page 18 of the Statement of Grounds, Opponent III has alleged that Claims 1 and 3 of the Patent as granted - in so far as they relate to TACI aspects - lack an inventive step in view of Master reference documents D1 and D9. Furthermore, Opponent II has alleged that the BCMA aspects of Claims 1 and 3 as granted are obvious in view of D10-D12. In addition, Opponent II has alleged that Claim 3j) as granted lacks an inventive step in view of D5-D8. These parts of Claims 1 and 3 as granted correspond to Claims 27-28, 30-32, 34-35 and 37-40 of Auxiliary Request 1.

10.71 None of the cited prior art provides any suggestion of the specific mechanism of action recited in these "use" claims - namely inhibition of ztnf4 activity or inhibition of BR43x2, TACI or BCMA receptor-ztnf4 engagements. In this regard, none of D1 or D9-D12 even mentions ztnf4, let alone identifies this molecule as a ligand for TACI or BCMA. With regard to D5-D8, none of these documents links ztnf4 to BR43x2, TACI or BCMA. Hence, Claims 27-28, 30-32, 34-35 and 37-40 of Auxiliary Request 1 are not obvious in view of the cited prior art.

10.72 With regard to Claims 27, 30, 34, 37 and 40, as discussed above, there is no suggestion in D1 or D9 of the specific medical conditions recited in these claims, and hence it would not be obvious that the recited compounds could be used to treat these conditions. Likewise, with regard to Claims 28, 31, 35 and 38, there is no disclosure in D10-D12 of any therapeutic uses (these are all merely academic papers) and hence treatment of the specific medical conditions recited in these claims would not have been obvious in view of D10-D12. With particular regard to Claims 31 and 38, we would mention that none of D10-D12 suggests an antibody that binds specifically to a polypeptide of SEQ ID NO: 8 (the antibodies used by Laabi *et al* were all raised against an N-terminally truncated BCMA-GST fusion). With regard to Claim 39, none of D6-D8 suggests the short (264 amino acid) sequence of SEQ ID NO: 18 and hence it would not be obvious to a skilled person reading D6-D8 to raise an antibody against this sequence. With regard to D5, this document fails to suggest any of the specific medical conditions recited in Claim 39.

10.73 Thus, Claims 27-28, 30-32, 34-35 and 37-40 of Auxiliary Request 1 all have an inventive step over D1 and D5-D12.

Claims 13-28 as granted

10.74 At the bottom of page 18 of the Statement of Grounds (through to the bottom of page 19) Opponent III has alleged that Claims 13-28 of the Patent as granted lack an inventive step in view of D1. The subject-matter of Claims 13-15 and 23 is not present in Auxiliary Request 1. The subject-matter of Claims 16-22 and 24-28 as granted has been incorporated throughout the "use" claims of Auxiliary Request 1.

10.75 D1 relates solely to TACI, and provides no suggestion of BCMA, BR43x2, SEQ ID NO: 10 or ztnf4. Hence those claims of Auxiliary Request 1 that do not relate to TACI molecules or anti-TACI antibodies are all inventive over D1, regardless of the medical conditions recited therein.

10.76 With regard to the "TACI" use claims of Auxiliary Request 1, these claims are all inventive over D1 as discussed above, since D1 does not suggest any specific ligand for TACI, let alone ztnf4. Thus, it would not have been obvious to a skilled person

reading D1 to use a TACI polypeptide or an anti-TACI antibody to inhibit ztnf4 activity or receptor-ztnf4 engagements. In particular, we would stress that inhibiting ztnf4 activity or inhibiting the ability of ztnf4 to engage its receptors is distinct from inhibiting TACI (as described in D1), since ztnf4 is an inventive selection from all the possible TACI ligands.

10.77 With particular regard to Claims 27, 30, 34, 37 and 40, none of the specific medical conditions recited in these claims is suggested by D1. By way of example, Opponent III has alleged that D1 describes treating "autoimmune diseases" and "inflammation" – however, these are broad definitions, which encompass a wide range of different medical conditions, including certain of the specific conditions recited in the claims of Auxiliary Request 1. Thus, a skilled person reading D1 would not consider it obvious that the recited compounds should (or even could) be used to treat these specific conditions.

10.78 Thus, the independent "use" claims of Auxiliary Request 1 (and all claims dependent thereon) are inventive over D1.

Claims 1 and 3, parts c) and h), as granted

10.79 In the middle of page 20 of the Statement of Grounds, Opponent III has raised a specific inventive step objection with regard to parts c) and h) of Claims 1 and 3 of the Patent as granted, in view of a combination of Master reference D1 with Master references D10-D12. Parts c) and h) of Claims 1 and 3 correspond to Claims 28, 31, 35 and 38 of Auxiliary Request 1.

10.80 Inventive step of Claims 28, 31, 35 and 38 of Auxiliary Request 1 has already been discussed above in relation to D1 and D10-D12. In brief, D1 provides no suggestion of a polypeptide comprising the BCMA extracellular domain, and also does not suggest any antibody that binds specifically to a polypeptide of SEQ ID NO: 8. Thus, uses of these compounds would not be obvious in view of D1. Likewise, D10-D12 also fail to suggest any antibody that specifically binds to a polypeptide of SEQ ID NO: 8. With regard to the medical conditions recited in Claims 28, 31, 35 and 38, none of these therapies are suggested by D10-D12, which are merely academic publications.

Furthermore, none of D1 or D10-D12 suggests any ligand for BCMA, let alone the specific ligand ztnf4. Hence, it would not be obvious in view of D1 or D10-D12 to use the recited compounds to inhibit ztnf4 activity or to inhibit BR43x2, TACI or BCMA receptor-ztnf4 engagements.

Claims 1, parts m) and n), and Claim 3, parts n) and o) as granted

10.81 Towards the bottom of page 20 of the Statement of Grounds, Opponent III has alleged that parts m) and n) of Claim 1, and parts n) and o) of Claim 3 as granted, lack an inventive step in view of the cited prior art. In more detail, Opponent III has alleged that use of the specific sequence fragments recited in these claims fails to solve any technical problem as compared to using the entire extracellular domain of BCMA. Claim 1m) and n) correspond to Claim 1f) - i) of Auxiliary Request 1. Claim 3n) and o) correspond to Claim 3i) - l) of Auxiliary Request 1.

10.82 As discussed in detail above, use of these specific BCMA fragments is inventive in view of the cited prior art. In brief, there is no suggestion in any of the cited BCMA prior art (D10-D13) of these specific N-terminal fragments, which embrace part or all of the BCMA cysteine rich pseudo repeat. Furthermore, it would not be obvious to a skilled person that such short fragments would have the required biological function. However, the present inventors have identified that these short fragments inhibit ztnf4 activity and/ or inhibit BR43x2, TACI or BCMA receptor-ztnf4 engagements, and can be used to treat the recited specific medical conditions. There is no suggestion in D10-D13 of any medical uses for BCMA (let alone for the short fragments) and hence the claimed therapeutic uses would not have been obvious over D10-D13. Thus, Claims 1f-i) and Claims 3i-l) of Auxiliary Request 1 are inventive.

Claim 1, parts a), e-f) and k); Claim 3, parts a) e-f) and l) as granted

10.83 On page 21 of the Statement of Grounds, Opponent III has alleged that the BR43x2 aspects of the present invention – namely Claim 1, parts a), e-f) and k); Claim 3, parts a) e-f) and l) and Claims 29-35 of the Patent as granted, lack an inventive step in view of the "TACI" prior art. These claims correspond to Claim 1a-c) and e); Claim 3a-c) and h); and Claims 17-23 of Auxiliary Request 1.

10.84 The inventiveness of the BR43x2 claims of Auxiliary Request 1 over the TACI prior art (D1 and D9) has been discussed in detail above. In brief, the recited BR43x2 polypeptide sequences would not have been obvious in view of the TACI prior art, which would lead a skilled away from a TACI isoform that lacks the first cysteine rich domain of TACI. Hence, a skilled person would not consider antibodies that specifically bind to these sequences to be obvious. In particular, the TACI prior art provides no suggestion that the recited BR43x2 polypeptides and antibodies inhibit ztnf4 activity or inhibit BR43x2, TACI or BCMA receptor-ztnf4 engagements. Furthermore, it would not be obvious to a skilled person in view of D1 or D9 to use these polypeptide and antibodies to treat the specific medical conditions recited in Claims 1 and 3 of Auxiliary Request 1. Thus, Claim 1a-c) and e); Claim 3a-c) and h); and Claims 17-23 of Auxiliary Request 1 have an inventive step over D1 and D9.

Claims 1 and 3, parts e) and f); and Claim 36, parts a) and b) as granted

10.85 Towards the bottom of page 21 of the Statement of Grounds, Opponent III has alleged that parts a) and b) of Claim 36 as granted lack an inventive step for the same reasons as alleged with regard to the BR43x2 aspects of Claims 1 and 3 as granted. Parts a) and b) of Claim 36 as granted correspond to parts a) and b) of Claim 24 of Auxiliary Request 1. Opponent II has also alleged that is would be obvious to use these antibodies for therapeutic uses, as recited in Claims 1 and 3 as granted.

10.86 In this regard, Opponent III is incorrect to assume that all antibodies that bind to TACI will also specifically bind to BR43x2. TACI and BR43x2 are distinct polypeptides, which differ from each other in the extracellular domain, and the anti-TACI antibodies of D1 and D9 would therefore provide no suggestion to a skilled person of an antibody that specifically binds to SEQ ID NO: 2 or 4. By way of example, the extracellular domains of BR43x2 and TACI fold in different ways (see Master reference D33) which would limit the extent or affinity to which anti-TACI antibodies would bind BR43x2, and vice versa. Thus, antibodies that specifically bind to a polypeptide of SEQ ID NO: 2 or 4 are not suggested by the TACI prior art (D1 and D9) and hence Claim 24 has an inventive step. Since the anti-BR43x2 antibodies are inventive, any therapeutic use of these antibodies, as recited in Claims 1 and 3 of Auxiliary Request 1, is also inventive.

Other Matters

Claims 1 and 3, part i); and Claim 36, part e) as granted

10.87 At the top of page 22 of the Statement of Grounds, Opponent III has alleged that antibodies or antibody fragments that bind specifically to a polypeptide of SEQ ID NO: 10 lack an inventive step in view of the anti-TACI antibodies described in D1. In particular, Opponent III has alleged that an inventive step is lacking for Claims 1 and 3, part i); and Claim 36, part e) as granted. These claims as granted correspond to Claims 1 and 3, part d), and Claim 24, part c) of Auxiliary Request 1.

10.88 As discussed in detail above, there is no suggestion in D1 of the particular sequence of SEQ ID NO: 10, and hence a skilled person reading D1 would not consider it obvious to prepare an antibody that specifically binds to a polypeptide of SEQ ID NO: 10. Furthermore, a skilled person reading D1 would not consider using an anti-SEQ ID NO: 10 antibody for inhibiting ztnf4 activity or receptor-ztnf4 engagements. In particular, it would not be obvious in view of D1 to use the anti-SEQ ID NO: 10 antibody to treat the specific medical conditions recited in Claims 1 and 3. Hence, Claims 1 and 3, part d), and Claim 24, part c) of Auxiliary Request 1 are inventive over the anti-TACI antibodies of D1.

Claim 3k) as granted

10.89 On page 22 of the Statement of Grounds, Opponent III has alleged that Claim 3k) of the Patent as granted lacks an inventive step in view of D1. Claim 3k) as granted corresponds to Claim 3g) of Auxiliary Request 1.

10.90 There is no suggestion of SEQ ID NO: 20 in D1, and hence it would not have been obvious to a skilled person reading D1 to raise an antibody against a polypeptide of SEQ ID NO: 20. Thus, Claim 3g) of Auxiliary Request 1 is inventive with regard to D1.

Claim 7b) as granted

10.91 On page 22 of the Statement of Grounds, Opponent III has alleged that Claim 7b) of the Patent as granted lacks an inventive step in view of D1. Granted Claim 7b) corresponds to Claim 46 of Auxiliary Request 1.

10.92 Claim 46 of Auxiliary Request 1 is dependent (ultimately) on any of Claims 27, 29, 32, 34, 36 or 40. In this regard, none of the specific therapeutic uses recited in Claims 27, 29, 32, 34, 36 or 40 are suggested by D1, and since D1 fails to suggest ztnf4, the mechanism of action recited in these claims would not be obvious in view of D1. Furthermore, there is no suggestion in D1 of making a fusion protein comprising the specific sequence amino acid residues 1-154 of SEQ ID NO: 6 (slightly shorter than the entire extracellular domain of TACI). In this regard, the specific fusion point of residue 154 of SEQ ID NO: 6 was carefully selected by the present inventors in order to include the TACI cysteine rich domains and as much of the 62 amino acid "stalk region" (between the cysteine rich domains and the transmembrane domain) as possible.

10.93 Furthermore, a TACI-Ig fusion protein having amino acids 1-154 of TACI, as recited in Claim 46 of Auxiliary Request 1 has been used successfully to inhibit the activity (eg. receptor-engagement) of ztnf4 *in vitro* – see Example 10 of the Patent. Administration of this TACI-Ig fusion ("TACI-FC4") to mouse models of spontaneous systemic lupus erythematosis (SLE) prior to onset of proteinuria reduced B cell numbers in a dose responsive manner – see Example 13 of the Patent (also Example 14). These findings are supported by Master reference D38, Figures 3c and 4, which illustrate a complete inhibition of ztnf4 stimulatory activity on human B cells *in vitro* in the presence of the recited TACI-Ig, and suppression of progression of SLE (in particular, proteinuria) in mouse models.

10.94 In addition, Master reference D40 confirms that transgenic mice that over-express a fusion protein of TACI residues 1-154 (TACI-Ig) have decreased numbers of B cells and decreased circulating antibody production – which is indicative of a role for this fusion protein in treatment of medical conditions including autoimmune diseases and B cell cancers.

10.95 These results would not have been obvious in view of D1. Hence, the use of the

specific fusion protein recited in Claim 46 of Auxiliary Request 1 would not have been obvious to a skilled person in view of D1, and Claim 46 of Auxiliary Request 1 is inventive over D1.

Claims 9-12 as granted

10.94 On page 22 of the Statement of Grounds, Opponent III has alleged that Claims 9-12 of the Patent as granted lack an inventive step in view of D1. Claims 9-12 as granted correspond to Claims 9-12 and 49-52 of Auxiliary Request 1.

10.95 Claims 9-12 and 49-52 of Auxiliary Request 1 are inventive over D1 by virtue of their dependency on other inventive fusion protein claims, and ultimately on inventive base Claims 1 and 3; and 27-29, 32, 34-36 and 40.

SUFFICIENCY OF DISCLOSURE – ARTICLE 83 EPC AND ARTICLE 100c EPC

Claims 1 and 3 as granted

10.96 At the bottom of page 22 of the Statement of Grounds, Opponent III has alleged that Claims 1 and 3 of the Patent as granted are insufficiently disclosed since they fail to recite any specific medical conditions to be treated by the medicament. In particular, Opponent III has alleged that the Patent does not teach how to identify medical conditions that fall within the scope of Claims 1 and 3 as granted.

10.97 This objection does not apply to Auxiliary Request 1, in which the independent "use" claims recite specific medical conditions to be treated by the recited compounds.

11 OBSERVATIONS IN REPLY TO OPPONENT IV

SECOND MEDICAL USE CLAIM FORMAT

11.1 In section 3 of the Statement of Grounds, Opponent IV has alleged that Claims 1 and 3 of the Patent as granted do not specify a therapy to be treated by the recited medicament, and thus are allegedly not in the correct "2nd medical use" claim format. Thus, Opponent IV has interpreted these claims as methods for making a medicament.

11.2 Opponent IV's objection against the 2nd medical use claims does not apply to Auxiliary Request 1, in which all the independent 2nd medical use claims recite specific medical conditions that are treatable using the recited medicaments.

NOVELTY – ARTICLE 54 EPC AND ARTICLE 100a EPC

Claim 1b) as granted

11.3 In point 6.1.1 of the Statement of Grounds, Opponent IV has alleged that Claim 1b) of the Patent as granted lacks novelty in view of Master reference D1 (referred to by Opponent IV as D4), which allegedly discloses using the extracellular domain of TACI in the manufacture of a medicament. Claim 1b) as granted corresponds to Claim 27 of Auxiliary Request 1.

11.4 D1 does not disclose any of the specific medical conditions recited in Claim 27, and hence Claim 27 of Auxiliary Request 1 is novel over D1.

Claim 1c) as granted

11.5 In point 6.1.2 of the Statement of Grounds, Opponent IV has alleged that Claim 1c) of the Patent as granted lacks novelty in view of Master reference D3 (referred to by Opponent IV as D6), which allegedly discloses uses of the BCMA extracellular domain. Claim 1c) as granted corresponds to Claim 28 of Auxiliary Request 1.

11.6 D3 fails to disclose any of the specific medical conditions recited in Claim 28, and hence Claim 28 of Auxiliary Request 1 is novel over D3.

Claim 1g) as granted

11.7 In point 6.1.3 of the Statement of Grounds, Opponent IV has alleged that Claim 1g) of the Patent as granted lacks novelty in view of Master reference D1 (referred to by Opponent IV as D4), which allegedly discloses using the anti-TACI antibodies for therapeutic uses. Claim 1g) as granted corresponds to Claim 30 of Auxiliary Request 1.

11.8 D1 does not disclose any of the specific medical conditions recited in Claim 30, and hence Claim 30 of Auxiliary Request 1 is novel over D1.

Claim 1h) as granted

11.9 In point 6.1.4 of the Statement of Grounds, Opponent IV has alleged that Claim 1h) of the Patent as granted lacks novelty in view of Master reference D3 (referred to by Opponent IV as D6), which allegedly discloses therapeutic uses of anti-BCMA antibodies. Claim 1h) as granted corresponds to Claim 31 of Auxiliary Request 1.

11.10 D3 fails to disclose any of the specific medical conditions recited in Claim 31, and hence Claim 31 of Auxiliary Request 1 is novel over D3.

Claim 1l) as granted

11.11 In point 6.1.5 of the Statement of Grounds, Opponent IV has alleged that Claim 1l) of the Patent as granted lacks novelty in view of Master reference D1 (referred to by Opponent IV as D4), which allegedly discloses using amino acid residues 1-166 of SEQ ID NO: 6 as a medicament. Claim 1l) as granted corresponds to Claim 32 of Auxiliary Request 1.

11.12 Claim 32 is novel over D1, which fails to disclose the mechanism of action of amino acid residues 1-166 of SEQ ID NO: 6. In more detail, D1 fails to disclose inhibition of

ztnf4 activity by amino acid residues 1-166 of SEQ ID NO: 6. Furthermore, there is no disclosure in D1 of using amino acid residues 1-166 of SEQ ID NO: 6 for the manufacture of a medicament for treating any medical condition by inhibiting ztnf4 activity. In particular, there is no disclosure in D1 of treating the specific medical conditions recited in Claim 32 by inhibiting ztnf4 activity. Thus, Claim 32 of Auxiliary Request 1 is novel over D1.

Claim 2 as granted

11.13 In point 6.2 of the Statement of Grounds, Opponent IV has alleged that Claim 2 of the Patent as granted lacks novelty over both Master references D1 and D3 (referred to as D4 and D6, respectively, by Opponent IV). Claim 2 as granted corresponds to Claims 2 and 33 of Auxiliary Request 1.

11.14 Claim 2 of Auxiliary Request 1 is dependent on Claim 1, which is novel over D1 and D3, since these citations fail to disclose any of the compounds recited for use in Claim 1. For the avoidance of doubt, there is no disclosure in D1 or D3 of any antibody/ antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 10. Thus, Claim 2 of Auxiliary Request 1 is novel over D1 and D3 by dependency on Claim 1.

11.15 Claim 33 depends on any of novel Claims 27-32 of Auxiliary Request 1. In more detail, D1 does not disclose any of the compounds recited for use in Claims 28-29 or 31. With regard to Claim 29, the "Prosite" consensus sequence recited in D1 is more flexible than (ie. broader than) the sequence of SEQ ID NO: 18 of the Patent. D1 also fails to disclose the specific medical conditions recited in Claims 27 and 30 of Auxiliary Request 1. As discussed above, Claim 32 of Auxiliary Request 1 is novel over D1. Thus Claim 33 of Auxiliary Request 1 is also novel over D1 by virtue of dependency.

11.16 Claim 33 is also novel over D3 by virtue of dependency on Claims 27-32 of Auxiliary Request 1. D3 fails to disclose any of the compounds recited in Claims 27, 30 or 32 and hence these claims are novel over D3. D3 also fails to disclose any of the specific medical conditions recited in Claims 28-29 or 31 of Auxiliary Request 1, and hence these claims are also novel over D3. Thus, Claim 33 of Auxiliary Request 1 is

novel by dependency.

Claim 3, parts b-d), g), h) and m) as granted

11.17 In point 6.3.1 of the Statement of Grounds, Opponent IV has alleged that Claim 3 of the Patent as granted lacks novelty over Master references D1 and D3 for the same reasons as given for Claim 1. Claim 3, parts b-d), g), h) and m) as granted correspond to Claims 34-38 and 40 of Auxiliary Request 1.

11.18 D1 does not disclose the compounds specified in Claims 35-36 or 38 of Auxiliary Request 1. Thus, these claims are novel over D1. With regard to Claims 34, 37 and 40 of Auxiliary Request 1, D1 does not disclose treating the specific medical conditions recited in these claims, and hence these claims are also novel over D1.

11.19 D3 does not disclose the specific compounds recited in Claims 34, 37 or 40 of Auxiliary Request 1, and hence these claims are novel over D3. With regard to Claims 35-36 and 38 of Auxiliary Request 1, D3 does not disclose treating the specific medical conditions recited in these claims, and hence these claims are also novel over D3.

Claim 3j) as granted

11.20 In point 6.3.2 of the Statement of Grounds, Opponent IV has alleged that Claim 3j) of the Patent as granted lacks novelty over Master reference D14 (referred to by Opponent IV as D5). Claim 3j) as granted corresponds to Claim 39 of Auxiliary Request 1.

11.21 Claim 39 of Auxiliary Request 1 is novel over D14, which fails to explicitly disclose the specific sequence of SEQ ID NO: 18, and thus provides no enabling disclosure of any antibody that binds specifically to a polypeptide of SEQ ID NO: 18. In more detail, the D14 ligand sequence is 285 amino acids long, whereas SEQ ID NO: 18 of the Patent is a truncated version of this sequence, being only 264 amino acids long. Thus the alleged provision in D14 of antibodies that bind to the D14 ztnf4 (BAFF) sequence is not enabling for the antibodies recited in Claim 39 of Auxiliary Request 1, which bind

specifically to a polypeptide of SEQ ID NO: 18. Thus, Claim 39 of Auxiliary Request 1 is novel over D14.

Furthermore, there is no disclosure in D14 of any of the specific medical conditions recited in Claim 39 of Auxiliary Request 1, let alone of using the specific antibody recited in Claim 39 for the manufacture of a medicament for treating these specific conditions. Thus, Claim 39 is novel over D14.

Claim 4a) as granted

11.22 In point 6.4.1 of the Statement of Grounds, Opponent IV has alleged that Claim 4a) of the Patent as granted lacks novelty over Master reference D3 (referred to by Opponent IV as D6). Claim 4a as granted corresponds to Claim 42 (part a) of Auxiliary Request 1.

11.23 Claim 42 (part a) of Auxiliary Request 1 depends on any of Claims 28-29 or 35-36, which, as discussed above, are novel over D3, which fails to recite the specific medical conditions recited in these claims. Thus, Claim 42 (part a) is novel over D3 by dependency.

Claim 4, parts c-e) as granted

11.24 In point 6.4.2 of the Statement of Grounds, Opponent IV has alleged that Claim 4c-e) of the Patent as granted lacks novelty over Master reference D1 (referred to by Opponent IV as D4). Parts c-e) of Claim 4 as granted correspond to Claim 41 of Auxiliary Request 1.

11.25 Claim 48 of Auxiliary Request 1 is dependent on any of Claims 27, 29, 32, 34, 36 or 40, which, as discussed above, are all novel over D1. Thus, Claim 41 of Auxiliary Request 1 is also novel over D1 by virtue of dependency.

Claim 4, parts f-h) as granted

11.26 In point 6.4.3 of the Statement of Grounds, Opponent IV has alleged that Claim 4f-h)

of the Patent as granted lacks novelty over Master reference D3 (referred to by Opponent IV as D6). Parts f-h) of Claim 4 as granted correspond to Claim 42 (parts b-d) of Auxiliary Request 1.

11.27 Claim 42 (parts b-d) of Auxiliary Request 1 depends on any of Claims 28-29 or 35-36, which, as discussed above, are novel over D3 by virtue of the specific medical conditions (and recited compounds – Claims 29 and 36). Thus, Claim 42 (parts b-d) is novel over D3 by dependency.

Claim 5b as granted

11.28 In point 6.5.1 of the Statement of Grounds, Opponent IV has alleged that Claim 5b) of the Patent as granted lacks novelty over Master reference D1 (referred to by Opponent IV as D4). Claim 5b) as granted corresponds to Claims 5b) and 43b) of Auxiliary Request 1.

11.29 Claim 5b) of Auxiliary Request 1 is dependent (ultimately) on either of Claims 1 or 3, which are novel over D1, since D1 does not disclose any of the compounds recited for use in these claims. Furthermore, by virtue of its dependency on Claim 4, Claim 5b) of Auxiliary Request 1 requires - in addition to amino acid residues 105-166 of SEQ ID NO: 6 - the presence in the first portion of a polypeptide of amino acid residues 25-58 of SEQ ID NO: 2. There is no disclosure in D1 of any fusion protein comprising a first portion containing both a polypeptide comprising amino acids 25-58 of SEQ ID NO: 2 and a polypeptide of amino acid residues 105-166 of SEQ ID NO: 6. Thus, Claim 5 (part b) is novel over D1.

11.30 Likewise, Claim 43b) of Auxiliary Request 1 depends (ultimately) on claims selected from Claims 27-29, 32, 34-36 or 40, which are all novel over D1 as discussed above by virtue of the recited compounds (Claims 28-29 and 35-36) or by virtue of the recited specific medical conditions (Claims 27, 34 and 40) or by virtue of the specific mechanism of action (Claim 32). Furthermore, by virtue of its dependency on Claim 41 or 42, Claim 5b) of Auxiliary Request 1 requires - in addition to amino acid residues 105-166 of SEQ ID NO: 6 - the presence in the first portion of a polypeptide as defined in parts a-c) of Claim 41 or a-d) of Claim 42. There is no disclosure in D1

of using any fusion protein comprising these combinations of sequence fragments in the first portion, and hence Claim 43 (part b) is novel over D1.

Claim 5c) as granted

11.31 In point 6.5.2 of the Statement of Grounds, Opponent IV has alleged that Claim 5c) of the Patent as granted lacks novelty over Master reference D3 (referred to by Opponent IV as D6). Claim 5c) as granted corresponds to Claims 5c) and 43c) of Auxiliary Request 1.

11.32 Claim 5c) of Auxiliary Request 1 depends (ultimately) on either of Claims 1 or 3, which are novel over D3, since D3 fails to disclose any of the compounds recited for use in these claims. Furthermore, by virtue of its dependency on Claim 4, Claim 5c) of Auxiliary Request 1 requires - in addition to amino acid residues 89-150 of SEQ ID NO: 8 - the presence in the first portion of a polypeptide of amino acid residues 25-58 of SEQ ID NO: 2. There is no disclosure in D3 of any fusion protein comprising a first portion containing both a polypeptide comprising amino acids 25-58 of SEQ ID NO: 2 and a polypeptide of amino acid residues 89-150 of SEQ ID NO: 8. Thus, Claim 5 (part c) is novel over D3.

11.33 Likewise, Claim 43c) of Auxiliary Request 1 depends (ultimately) on Claims selected from Claims 27-29, 32, 34-36 or 40, which are all novel over D3 as discussed above, by virtue of the recited compounds (Claims 27, 29, 32, 34, 36 and 40) and the recited specific medical conditions (Claims 28 and 35). Furthermore, by virtue of its dependency on Claim 41 or 42, Claim 5c) of Auxiliary Request 1 requires - in addition to amino acid residues 89-150 of SEQ ID NO: 8 - the presence in the first portion of a polypeptide as defined in parts a-c) of Claim 48 or a-d) of Claim 42. There is no disclosure in D3 of using any fusion protein comprising these combinations of sequence fragments in the first portion, and hence Claim 43 (part c) is novel over D1.

Claim 6b) as granted

11.34 In point 6.6.1 of the Statement of Grounds, Opponent IV has alleged that Claim 6b) of the Patent as granted lacks novelty over Master reference D1 (referred to by

Opponent IV as D4). Claim 6b) as granted corresponds to Claim 44 of Auxiliary Request 1.

11.35 Claim 44 of Auxiliary Request 1 depends on Claim 48, and ultimately on any of Claims 27, 29, 32, 34, 36 or 40. All these base claims are novel over D1 as discussed above, since D1 fails to recite the specific medical conditions recited in these claims. Thus, Claim 44 of Auxiliary Request 1 is also novel over D1, by virtue of dependency.

Claim 6c) as granted

11.36 In point 6.6.2 of the Statement of Grounds, Opponent IV has alleged that Claim 6c) of the Patent as granted lacks novelty in view of Master reference D3 (referred to by Opponent IV as D6). Claim 6c) as granted corresponds to Claim 45 of Auxiliary Request 1.

11.37 Claim 45 of Auxiliary Request 1 depends on Claim 42, and ultimately on any of Claims 28-29 or 35-36. All these base claims are novel over D3, since D3 fails to recite the specific medical conditions recited in these claims. Thus, Claim 45 of Auxiliary Request 1 is also novel over D3, by virtue of dependency.

Claim 8 as granted

11.38 In point 6.7 of the Statement of Grounds, Opponent IV has alleged that Claim 8 of the Patent as granted lacks novelty in view of Master reference D1 (referred to by Opponent IV as D4) and Master reference D3 (referred to by Opponent IV as D6). Claim 8 as granted corresponds to Claims 8 and 48 of Auxiliary Request 1.

11.39 Both Claims 8 and 48 of Auxiliary Request 1 depend on Claims that are novel over D1 and D3. In more detail, Claim 8 depends ultimately on either of Claims 1 or 3, which are novel over D1 and D3, which do not disclose any of the compounds recited for use in these claims. Claim 48 depends ultimately on any of Claims 27-29, 32, 34-36 or 40, which are novel over D1 and D3 by virtue of the recited compounds and/ or specific medical conditions, or by virtue of the specific mechanism of action. Hence, Claims 8 and 48 of Auxiliary Request 1 are also novel over D1 and D3 by virtue of

dependency.

Claim 9 as granted

11.40 In point 6.8 of the Statement of Grounds, Opponent IV has alleged that Claim 9 of the Patent as granted lacks novelty in view of Master reference D3 (referred to by Opponent IV as D6). Claim 9 as granted corresponds to Claims 9 and 49 of Auxiliary Request 1.

11.41 Claims 9 and 49 of Auxiliary Request 1 depend on Claims that are novel over D3. In more detail, Claim 9 depends ultimately on either of Claims 1 or 3 - which are novel over D3 since D3 fails to disclose any of the compounds recited for use in these claims. Claim 49 depends ultimately on any of Claims 27-29, 32, 34-36 or 40, which are novel over D3 by virtue of the specific medical conditions (Claims 28 and 35) or by virtue of the recited compounds (Claims 27, 29, 32, 34, 36 and 40). Hence, Claims 9 and 49 of Auxiliary Request 1 are also novel over D3 by virtue of dependency.

Claim 10 as granted

11.42 In point 6.9 of the Statement of Grounds, Opponent IV has alleged that Claim 10 of the Patent as granted lacks novelty in view of Master reference D3 (referred to by Opponent IV as D6). Claim 10 as granted corresponds to Claims 10 and 50 of Auxiliary Request 1.

11.43 Claims 10 and 50 of Auxiliary Request 1 are novel over D3 by virtue of dependency. In more detail, Claim 10 depends ultimately on either of Claims 1 or 3 - which are novel over D3 since D3 fails to disclose any of the compounds recited for use in these claims. Claim 50 depends ultimately on any of Claims 27-29, 32, 34-36 or 40, which are novel over D3 as discussed above. Hence, Claims 10 and 50 of Auxiliary Request 1 are also novel over D3 by dependency.

Claims 13-15 as granted

11.44 In points 6.10-6.12 of the Statement of Grounds, Opponent IV has alleged that Claims

13-15 of the Patent as granted lack novelty in view of Master reference D1 (referred to by Opponent IV as D4). The subject-matter of Claims 13-15 as granted is not present in Auxiliary Request 1.

Claims 16 and 17 as granted

11.45 In points 6.13-6.14 of the Statement of Grounds, Opponent IV has alleged that Claims 16 and 17 of the Patent as granted lacks novelty in view of Master reference D1 (referred to by Opponent IV as D4). The subject-matter of Claims 16-17 as granted has been incorporated into Claims 1, 3 and 32 of Auxiliary Request 1.

11.46 As discussed above, D1 does not disclose any of the specific compounds recited for use in Claims 1 and 3, and does not disclose the mechanism of action of amino acid residues 1-166 of SEQ ID NO: 6, as recited in Claim 32. Thus, Claims 1, 3 and 32 of Auxiliary Request 1 are novel over D1.

Claim 18 as granted

11.47 In point 6.15 of the Statement of Grounds, Opponent IV has alleged that Claim 18 of the Patent as granted - insofar as it relates to systemic lupus erythematosis, myasthenia gravis and rheumatoid arthritis - lacks novelty in view of Master reference D1 (referred to by Opponent IV as D4). The "systemic lupus erythematosis", "myasthenia gravis" and "rheumatoid arthritis" aspects of Claim 18 as granted are found in Claims 13, 28, 31, 35, 38 and 39 (myasthenia gravis only) and 53 of Auxiliary Request 1.

11.48 Claim 13 of Auxiliary Request 1 is novel over D1 by virtue of dependency on Claims 1 or 3 (which are novel by virtue of the recited compounds); and Claim 53 is novel over D1 by virtue of dependency on Claim 32 (which is novel over D1 by virtue of the recited specific mechanism of action). With regard to Claims 28, 31, 35, 38 and 39 of Auxiliary Request 1, these claims are also novel over D1, which does not disclose the specific compounds recited in these claims.

Claim 19 as granted

11.49 In point 6.16 of the Statement of Grounds, Opponent IV has alleged that Claim 19 of the Patent as granted - insofar as it relates to end stage renal disease – lacks novelty over Master reference D1 (referred to by Opponent IV as D4). The "end stage renal failure" aspect of Claim 19 as granted has been incorporated into Claims 1, 3, 28, 31, 35 and 38-39 of Auxiliary Request 1.

11.50 Claims 1, 3, 28, 31, 35 and 38-39 of Auxiliary Request 1 are all novel over D1, since D1 fails to disclose the specific compounds recited in these claims.

Claim 20 as granted

11.51 In point 6.17 of the Statement of Grounds, Opponent IV has alleged that Claim 20 of the Patent as granted - insofar as it relates to glomerulonephritis - lacks novelty over Master reference D1 (referred to by Opponent IV as D4). The "glomerulonephritis" aspect of Claim 20 as granted has been incorporated into Claims 14 and 55 of Auxiliary Request 1.

11.52 Claims 14 and 55 of Auxiliary Request 1 depend on Claims 1 or 3, and Claims 28, 31, 35 or 38-39, respectively. These claims are novel over D1 as discussed above, since D1 fails to disclose any of the compounds recited for use in these claims. Thus, Claims 14 and 55 of Auxiliary Request 1 are also novel, by dependency.

Claim 21 as granted

11.53 In point 6.18 of the Statement of Grounds, Opponent IV has alleged that Claim 21 of the Patent as granted - insofar as it relates to multiple myelomas and lymphomas – lacks novelty in view of Master reference D1. The "multiple myelomas" and "lymphomas" aspects of Claim 21 as granted have been incorporated into Claims 1, 3, 28, 31, 32, 35 and 38 of Auxiliary Request 1.

11.54 As discussed above, all of Claims 1, 3, 28, 31, 32, 35 and 38 of Auxiliary Request 1 are novel over D1, since none of the compounds recited in Claims 1, 3, 28, 31, 35

and 38 are disclosed in D1, and the mechanism of action recited in Claim 32 is not disclosed in D1.

Claim 23 as granted

11.55 In point 6.19 of the Statement of Grounds, Opponent IV has alleged that Claim 23 of the Patent as granted lacks novelty in view of Master reference D1. The subject-matter of Claim 23 as granted is not present in Auxiliary Request 1.

Claims 24 and 25 as granted

11.56 In points 6.20-6.21 of the Statement of Grounds, Opponent IV has alleged that Claims 24-25 of the Patent as granted lack novelty in view of Master reference D1. The subject-matter of Claims 24-25 as granted has been incorporated into Claims 1, 3, 28, 31, 35 and 38 of Auxiliary Request 1, which are novel over D1 by virtue of the recited compounds.

Claim 27 as granted

11.57 In point 6.22 of the Statement of Grounds, Opponent IV has alleged that Claim 27 of the Patent as granted lacks novelty in view of Master reference D1. The subject-matter of Claim 27 as granted has been incorporated into Claims 1 and 3 of Auxiliary Request 1.

11.58 D1 does not disclose any of the specific compounds recited for use in Claims 1 and 3 of Auxiliary Request 1, and hence these claims are novel over D1.

Claim 36c) as granted

11.59 In point 6.23.1 of the Statement of Grounds, Opponent IV has alleged that Claim 36 of the Patent as granted – to the extent that it relates to an antibody or antibody fragment that binds specifically to a polypeptide of SEQ ID NO: 6 - lacks novelty in view of Master reference D1 (referred to by Opponent IV as D4). Claim 36 as granted corresponds to Claim 24 of Auxiliary Request 1.

11.60 D1 does not disclose any of the antibodies recited in Claim 24 of Auxiliary Request 1. In more detail, none of the anti-TACI antibodies described in D1 would bind specifically to a polypeptide of SEQ ID NO: 2, 4 or 10. There is no disclosure in D1 of any of the recited antibodies, and hence Claim 24 of Auxiliary Request 1 is novel over D1.

Claim 36d) as granted

11.61 In point 6.23.2 of the Statement of Grounds, Opponent IV has alleged that Claim 36 of the Patent as granted – to the extent that it relates to an antibody or antibody fragment that binds specifically to a polypeptide of SEQ ID NO: 8 - lacks novelty in view of Master reference D3 (referred to by Opponent IV as D6). Claim 36 as granted corresponds to Claim 24 of Auxiliary Request 1.

11.62 D3 fails to disclose any of the antibodies recited in Claim 24 of Auxiliary Request 1. In more detail, none of the anti-BCMA antibodies described in D3 are raised against an antigen that is a polypeptide of SEQ ID NO: 2, 4 or 10. Thus, none of the D3 antibodies would bind specifically to a polypeptide of SEQ ID NO: 2, 4 or 10. In this regard, it would be a matter of routine for a skilled person to identify a "specifically binding" antibody (see paragraph 0073 of the Patent specification). Thus, the presently claimed antibodies are not disclosed in D3, and Claim 24 of Auxiliary Request 1 is therefore novel over D3.

Claims 37 and 38 as granted

11.63 In points 6.24-6.25 of the Statement of Grounds, Opponent IV has alleged that Claims 37-38 of the Patent as lack novelty in view of Master reference D1 (referred to by Opponent IV as D4) and Master reference D3 (referred to by Opponent IV as D6). Claims 37-38 as granted corresponds to Claims 25-26 of Auxiliary Request 1.

11.64 Claims 25-26 of Auxiliary Request 1 depend on Claim 24, which is novel over both D1 and D3 as discussed above, since neither of these prior art documents discloses the recited antibodies. Thus, Claims 25-26 are also novel over D1 and D3 by virtue of

this dependency.

INVENTIVE STEP – ARTICLE 56 EPC AND ARTICLE 100a EPC

Claim 1, parts d) and i) as granted

11.65 In point 7.1.1 of the Statement of Grounds, Opponent IV has alleged that parts d) and i) of Claim 1 of the Patent as granted, relating to a polypeptide of SEQ ID NO: 10 and an antibody or antibody fragment that binds specifically to this sequence, lack an inventive step in view of Master reference D12 (referred to by Opponent IV as D2) and Master reference D1 (referred to by Opponent IV as D4). Parts d) and i) of Claim 1 as granted correspond to Claims 1d) and 29 of Auxiliary Request 1.

11.66 As discussed above, D1 does not suggest using a polypeptide comprising the sequence of SEQ ID NO: 10 to treat any of the specific medical conditions recited in Claim 29 of Auxiliary Request 1. In particular, the use of this polypeptide to inhibit ztnf4 activity is not suggested by D1. Likewise, D12 (which is merely an academic publication) fails to suggest any biological mechanism of action or therapeutic use of a polypeptide comprising SEQ ID NO: 12. Hence, Claim 29 of Auxiliary Request 1 is inventive over D1 and D12.

11.67 Also as discussed above, D12 fails to suggest any antibodies, let alone antibodies that specifically bind to a polypeptide of SEQ ID NO: 10. D12 also fails to suggest any therapeutic use to which such an antibody could be put. Furthermore, since D1 does not provide any suggestion of SEQ ID NO: 10 (see above), it would not be obvious in view of D1 to raise an antibody that binds specifically to a polypeptide of SEQ ID NO: 10. The specific therapeutic uses of this inventive antibody, as recited in Claim 1, would also not be obvious in view of D1. Claim 1d) therefore has an inventive step with regard to D1 and D12.

Claim 1, parts b) and g) as granted

11.68 In point 7.1.2 of the Statement of Grounds, Opponent IV has alleged that parts b) and g) of Claim 1 of the Patent as granted, relating to a soluble polypeptide comprising the

extracellular domain of TACI, and an antibody or antibody fragment that binds specifically to a polypeptide of SEQ ID NO: 6, lack an inventive step in view of a combination of Master reference D9 (referred to by Opponent IV as D1) with unspecified "common general knowledge". Parts b) and g) of Claim 1 as granted correspond to Claims 27 and 30 of Auxiliary Request 1.

11.69 D9 is merely an academic publication, which fails to suggest either the specific mechanism of action of the recited soluble polypeptide or antibody, or any therapeutic use of these compounds. Thus, as discussed above, D9 would be a poor starting point for a skilled person. The alleged vague reference in D9 to a link with immune cells would not suggest to a skilled person (even in view of the unidentified common general knowledge) that the recited compounds could be used as therapeutics. In particular, treatment of the specific medical conditions recited in Claims 27 and 30 of Auxiliary Request 1 would not be obvious to a skilled person. Hence, these claims are inventive over D9 and the common general knowledge.

Claim 2 as granted

11.70 In point 7.2 of the Statement of Grounds, Opponent IV has alleged that the subject-matter of Claim 2 of the Patent as granted – namely, use wherein the mammal is a primate – lacks an inventive step in view of Master reference D9 (referred to as D1 by Opponent IV). Claim 2 as granted corresponds to Claims 2 and 33 of Auxiliary Request 1.

11.71 Dependent Claims 2 and 33 of Auxiliary Request 1 are inventive over D9 by virtue of their dependency on inventive Claims 1, 3 and 27-32. These base claims all recite at least one of a) non-TACI compounds that are not suggested by D9; b) a specific mechanism of action based on inhibition of ztnf4, which is not suggested by D9; or c) the treatment of specific medical conditions that are not suggested by the merely academic disclosure of D9. Hence, dependent Claims 2 and 33 of Auxiliary Request 1 are both inventive with respect to D9.

Claim 3, parts b), d), g), i) and m) as granted

11.72 In point 7.3 of the Statement of Grounds, Opponent IV has alleged that parts b), d), g), i) and m) of Claim 3 of the Patent as granted lack an inventive step for the same reasons as presented by Opponent IV with regard to corresponding parts of Claim 1. Parts b), d), g), i) and m) of Claim 3 as granted correspond to Claims 3d), 34, 36, 37 and 40 of Auxiliary Request 1.

11.73 Claims 3d), 34 and 36-37 of Auxiliary Request 1 are inventive over D1, D12 and D9 for the same reasons as given above with regard to Claims 1d), 27 and 29-30 of Auxiliary Request 1. Claim 40 of Auxiliary Request 1 is also inventive since D12 fails to suggest amino acids 1-166 of SEQ ID NO: 6; and D1 and D9 does not suggest treating any of the specific medical conditions recited in Claim 40.

Claim 4, parts c-e) as granted

11.74 In point 7.4 of the Statement of Grounds, Opponent IV has alleged that Claim 4, parts c-e) of the Patent as granted lack an inventive step in view of Master reference D9 (referred to by Opponent IV as D1). Parts c-e) of Claim 4 as granted correspond to Claim 41 of Auxiliary Request 1.

11.75 Claim 41 of Auxiliary Request 1 depends on any of Claims 27, 29, 32, 34, 36 or 40, which are all inventive over D1. In particular, the specific mechanisms of action or medical conditions recited in these base claims would not have been obvious in view of D1. Hence, Claim 41 of Auxiliary Request 1 is also inventive by virtue of dependency.

Claim 5 as granted

11.76 In point 7.5 of the Statement of Grounds, Opponent IV has alleged that Claim 5 of the Patent as granted lacks an inventive step in view of Master references D9 (referred to by Opponent IV as D1) and D8 (referred to by Opponent IV as D3). Claim 5 as granted corresponds to Claims 5 and 43 of Auxiliary Request 1.

11.77 There is no suggestion in the purely academic disclosure of D9 of any therapeutic uses of fusion proteins. In particular, treatment of the specific medical conditions

recited in inventive Claims 1, 3, 27-29, 32, 34-36 or 40 - on which Claims 5 and 43 depend – would not have been obvious in view of the limited disclosure of D9. With regard to D8, this document relates solely to ztnf4 and fails to suggest any of the specific fusion proteins recited in Claims 5 and 43 of Auxiliary Request 1. Thus, Claims 5 and 43 of Auxiliary Request 1 are inventive over D9 and D8.

Claim 6b) as granted

11.78 In point 7.6 of the Statement of Grounds, Opponent IV has alleged that Claim 6b) of the Patent as granted lacks an inventive step in view of Master reference D9 (referred to by Opponent IV as D1) and unspecified "common general knowledge". Claim 6b) as granted corresponds to Claim 44 of Auxiliary Request 1.

11.79 As discussed above with regard to Claim 50, Claim 51 is inventive in view of D9, which fails to suggest using a fusion protein to treat any medical condition, let alone the specific conditions recited in Claims 27, 29, 32, 34, 36 or 40, on which Claim 44 (ultimately) depends. In particular, vague references in the prior art to "possible uses in immune modulation" would not suggest to a skilled person that a fusion protein comprising the extracellular domain of TACI would be therapeutically useful. Hence, Claim 44 of Auxiliary request 1 has an inventive step.

Claim 7 as granted

11.80 In point 7.7 of the Statement of Grounds, Opponent IV has alleged that Claim 7 of the Patent as granted - insofar as it relates to a fusion protein as recited in part b) of Claim 7 - lacks an inventive step in view of Master reference D1 (referred to by Opponent IV as D4). Claim 7b) as granted corresponds to Claim 46 of Auxiliary Request 1.

11.81 There is no suggestion in D1 of any fusion protein containing a first domain consisting of amino acids 1-154 of SEQ ID NO: 6. Hence, Claim 46 of Auxiliary Request 1 would not have been obvious to a skilled person in view of D1. Furthermore, none of the specific medical conditions recited in Claims 27, 29, 32, 34, 36 or 40 – on which Claim 46 ultimately depends – are suggested in D1. Hence, Claim 46 of Auxiliary Request 1

is inventive over D1.

Claim 8 as granted

11.82 In point 7.8 of the Statement of Grounds, Opponent IV has alleged that Claim 8 of the Patent as granted lacks an inventive step in view of Master reference D8 (referred to by Opponent IV as D3). Claim 8 as granted corresponds to Claims 8 and 48 of Auxiliary Request 1.

11.83 D8 relates solely to ztnf4 and fails to suggest any of the specific fusion proteins recited in the claims of Auxiliary Request 1. Furthermore, it would not have been obvious in view of D8 to use the recited fusion proteins to treat the specific medical conditions recited in these claims. Hence, dependent Claims 8 and 48 of Auxiliary Request 1 are inventive over D8.

Claim 9 as granted

11.84 In point 7.9 of the Statement of Grounds, Opponent IV has alleged that Claim 9 of the Patent as granted lacks an inventive step in view of Master reference D8 (referred to by Opponent IV as D3). Claim 9 as granted corresponds to Claims 9 and 49 of Auxiliary Request 1.

11.85 Fusion protein Claims 9 and 49 of Auxiliary Request 1 are inventive over D8 for the same reasons as given above with regard to Claims 8 and 48 of Auxiliary Request 1.

Claim 10 as granted

11.86 In points 7.10 and 7.11 of the Statement of Grounds, Opponent IV has alleged that Claims 10 and 11 of the Patent as granted lack an inventive step. Claim 10 as granted corresponds to Claims 10 and 50 of Auxiliary Request 1, and Claim 11 as granted corresponds to Claims 11 and 51 of Auxiliary Request 1.

11.87 Claims 10, 11, 50 and 51 of Auxiliary Request 1 are dependent on inventive fusion protein Claims 4, 41 and 42, and ultimately on any of inventive use Claims 1, 3, 27-29,

32, 34-36 and 40. Hence, these claims are inventive by virtue of dependency.

Claim 12 as granted

11.88 In point 7.12 of the Statement of Grounds, Opponent IV has alleged that Claim 12 of the Patent as granted is unclear and thus merely states the obvious. Claim 12 as granted corresponds to Claims 12 and 52 of Auxiliary Request 1.

11.90 Opponent IV will, no doubt, be aware that a lack of clarity under Article 84 EPC is not a ground of Opposition under Article 100 EPC, and hence Opponent IV's allegation is in itself unclear. However, in the event that this objection is intended to be an allegation of lack of inventive step of Claim 12 as granted, we confirm that corresponding Claims 12 and 52 of Auxiliary Request 1 are inventive over the prior art for the same reasons as given above with regard to Claims 10, 11, 50 and 51 of Auxiliary Request 1.

Claim 13-15 as granted

11.91 In points 7.13-7.15 of the Statement of Grounds, Opponent IV has alleged that Claims 13-15 of the Patent as granted lack an inventive step in view of Master reference D1 (referred to by Opponent IV as D4). The subject-matter of Claims 13-15 as granted is absent from Auxiliary Request 1.

Claim 16 as granted

11.92 In point 7.16 of the Statement of Grounds, Opponent IV has alleged that Claim 16 of the Patent as granted lacks an inventive step. The subject-matter of Claim 16 as granted has been incorporated into Claims 1, 3 and 32 of Auxiliary Request 1, which are all inventive over the cited prior art (as discussed in detail above) by virtue of the recited compounds and the recited mechanism of action.

Claims 17-25 as granted

11.93 In point 7.17 of the Statement of Grounds, Opponent IV has alleged that the subject-

matter of dependent Claims 17-25 of the Patent as granted lacks an inventive step in view of Master reference D1 (referred to by Opponent IV as D4). The subject-matter of Claim 23 is not present in Auxiliary Request 1. The subject-matter of Claims 17-25 as granted has been incorporated into Claims 1, 3, 13-14, 27-32, 34-40, 53 and 55 of Auxiliary Request 1.

11.94 As discussed in detail above, independent Claims 1 and 3 of Auxiliary Request 1 are inventive over D1, which does not suggest any of the compounds recited in these claims. Claims 13-14 also have an inventive step over D1, by virtue of their dependency on Claims 1 or 3. Also as discussed above, the subject-matter of Claims 27-32 and 34-40 would not be considered obvious by a skilled person in view of D1, and hence these claims have an inventive step. In this regard, general references in D1 to treating general autoimmune diseases and cancers would not make it obvious to treat the specific medical conditions recited in these claims. Thus, dependent Claims 53 and 55 also have an inventive step over D1.

Claim 28 as granted

11.95 In point 7.18 of the Statement of Grounds, Opponent IV has alleged that dependent Claim 28 of the Patent as granted lacks an inventive step. In particular, Opponent III has alleged that the specific inflammatory conditions recited in Claim 28 as granted are merely an arbitrary selection of diseases. The subject-matter of Claim 28 as granted has been incorporated into Claims 16, 27-31 and 34-40 of Auxiliary Request 1.

11.96 Claim 16 is dependent on either of Claims 1 or 3, which are inventive over the cited prior art by virtue of the recited compounds. Hence, Claim 16 is also inventive due to its dependency. Claims 27-31 and 34-40 are also inventive since, as discussed above, none of the cited prior art suggests the claimed, specific, therapeutic uses of the recited compounds.

Claim 36e) as granted

11.97 In point 7.19 of the Statement of Grounds, Opponent IV has alleged that Claim 36 as

granted – insofar as it relates to antibodies that specifically binds to a polypeptide of SEQ ID NO: 10 – lacks an inventive step in view of Master reference D9 (referred to by Opponent IV as D1). Claim 36e) as granted corresponds to Claim 24c) of Auxiliary Request 1.

11.98 D9 fails to provide any suggestion of a polypeptide having the sequence of SEQ ID NO: 10, let alone any antibody that specifically binds to this polypeptide. In particular, it would not have been obvious to a skilled person reading D9 that these antibodies are therapeutically useful. Hence, the pharmaceutical composition recited in Claim 24c) of Auxiliary Request 1 is inventive over D9.

Claim 37 as granted

11.99 In point 7.20 of the Statement of Grounds, Opponent IV has alleged that the subject-matter of dependent Claim 37 lacks an inventive step in view of Master reference D1 (referred to by Opponent IV as D4). In this regard, the reference to Claim 35 of the Patent in point 7.20 would appear to be a typographical error, since Claim 35 as granted does not relate to antibody compositions. Claim 37 as granted corresponds to Claim 25 of Auxiliary Request 1.

11.100 Claim 25 of Auxiliary Request 1 depends on Claim 24, which is inventive in view of D1 by virtue of the recited antibodies, which specifically bind a polypeptide of SEQ ID NO: 2, 4 or 10. Hence, Claim 25 of Auxiliary Request 1 is also inventive, by virtue of dependency.

Claim 38 as granted

11.101 In point 7.21 of the Statement of Grounds, Opponent IV has alleged that Claim 38 as granted lacks an inventive step in view of Master reference D1 (referred to by Opponent IV as D4). Claim 38 as granted corresponds to Claim 26 of Auxiliary Request 1.

11.102 Claim 26 of Auxiliary Request 1 depends on Claim 24, which as discussed above is inventive in view of D1 by virtue of the recited specifically binding antibodies. Hence,

Claim 26 of Auxiliary Request 1 is also inventive, by virtue of dependency.

SUFFICIENCY OF DISCLOSURE- ARTICLE 83 EPC AND ARTICLE 100c EPC

Claim 1d) as granted

11.103 In point 8.1.2 of the Statement of Grounds, Opponent IV has alleged that Claim 1d) of the Patent as granted, relating to the use of a polypeptide comprising the sequence of SEQ ID NO: 10, is insufficiently disclosed in the Patent specification as filed. In particular, Opponent IV has alleged that SEQ ID NO: 10 embraces a large number of sequences and that not all of these would have the desired biological function. Furthermore, Opponent IV has alleged that a polypeptide of SEQ ID NO: 10 would not bind ztnf4. Claim 1d) as granted corresponds to Claim 29 of Auxiliary Request 1.

11.104 Opponent IV is incorrect to allege that a polypeptide of SEQ ID NO: 10 would not have the desired function - namely, inhibiting ztnf4 activity. In this regard, SEQ ID NO: 10 is based on the cysteine rich domain of the novel polypeptide BR43x2, which is a receptor for ztnf4. In particular, the 6 non-variable key cysteine residues of SEQ ID NO: 10 (corresponding to residues 25, 40, 43, 47, 54 and 58 of BR43x2), collectively form a binding site for binding ztnf4. Since all polypeptides of SEQ ID NO: 10 have the above-mentioned 6-cysteine core structure, all polypeptides comprising the sequence of SEQ ID NO: 10 would bind ztnf4. No evidence to counter this has been provided by Opponent IV.

11.105 By binding ztnf4, a polypeptide of SEQ ID NO: 10 inhibits the activity of ztnf4 - for example by preventing ztnf4 from binding to its receptor. Hence, Opponent IV is incorrect to allege that the recited polypeptide would not have the desired biological function.

11.106 Thus, Claim 1d) of the Patent as granted, relating to the use of a polypeptide comprising the sequence of SEQ ID NO: 10, is insufficiently disclosed in the Patent specification as filed.

Claim 1i) as filed

11.107 In point 8.1.3 of the Statement of Grounds, Opponent IV has alleged that Claim 1i) of the Patent as granted, relating to the use of an antibody or antibody fragment that binds specifically to a polypeptide comprising the sequence of SEQ ID NO: 10, is insufficiently disclosed in the Patent specification as filed. In particular, Opponent IV has alleged that Claim1i) as granted embraces a large number of antibodies, not all of which would have the desired biological function – namely, inhibiting ztnf4 activity. Claim 1i) as granted corresponds to Claim 1d) of Auxiliary Request 1.

11.108 The SEQ ID NO: 10 polypeptide sequence contains 6 non-variable key cysteine residues (corresponding to residues 25, 40, 43, 47, 54 and 58 of the BR43x2 polypeptide - see paragraph 0019 of the Patent specification as granted), which are involved in interactions with ztnf4. In more detail, these 6 cysteine residues collectively form an important antigenic structure for generation of an anti-SEQ ID NO: 10 antibody that has the ability to inhibit ztnf4 activity (ie. by inhibiting the ability of ztnf4 to bind to a polypeptide sequence of SEQ ID NO: 10).

11.109 In this regard, Master reference D35 (by the Proprietor) describes antibodies that specifically bind to a polypeptide of SEQ ID NO: 10. In particular, the monoclonal antibody 255.7 discussed in Examples 1-3 of D35 was raised against a polypeptide antigen having a sequence of SEQ ID NO: 10. As described in Example 1, this antibody was particularly useful for treating multiple myeloma *in vivo*, and was effective for inhibiting proliferation of Burkitt's lymphoma and multiple myeloma cell lines *in vitro*. Thus, D35 confirms that the recited antibodies, which specifically bind to a polypeptide of SEQ ID NO: 10, inhibit the activity of ztnf4.

11.110 Thus, the recited therapeutic uses of an antibody or antibody fragment that binds specifically to a polypeptide comprising the sequence of SEQ ID NO: 10, are sufficiently disclosed in the Patent specification as filed.

Claim 2 as filed (when dependent on Claim 1, parts d) and i) as granted)

11.111 In point 8.1.4 of the Statement of Grounds, Opponent IV has alleged that Claim 2 of

the Patent as granted lacks sufficient disclosure for the same reasons as provided with respect to Claim 1, parts d) and i), above. Claim 2 as granted corresponds to Claims 2 and 33 of Auxiliary Request 1.

11.112 Dependent Claims 2 and 33 are sufficiently disclosed for the same reasons as given above with regard to Claim 1, parts d) and i) as granted, since antibodies or antibody fragments that bind specifically to a polypeptide comprising the sequence of SEQ ID NO: 10, and the recited therapeutic uses thereof, are sufficiently disclosed in the Patent specification as filed.

Claim 3, parts d) and i) as granted

11.113 In point 8.1.5 of the Statement of Grounds, Opponent IV has alleged that parts d) and i) of Claim 3 of the Patent as granted lack sufficient disclosure for the same reasons as provided with respect to Claim 1, parts d) and i), above. Claim 3d) and 3i) as granted correspond to Claims 36 and 3d), respectively, of Auxiliary Request 1.

11.114 Claims 3d) and 3i) as granted are sufficiently disclosed for the same reasons as given above with regard to Claim 1, parts d) and i) as granted, since antibodies or antibody fragments that bind specifically to a polypeptide comprising the sequence of SEQ ID NO: 10, and the recited therapeutic uses thereof, are sufficiently disclosed in the Patent specification as filed.

Claim 4a) as granted

11.115 In point 8.1.6 of the Statement of Grounds, Opponent IV has alleged that Claim 4a) of the Patent as granted, relating to a fusion protein in which the first portion comprises the sequence SEQ ID NO: 8, is insufficiently disclosed. In particular, Opponent IV has alleged that the recited fusion protein could not be made and/ or would not have the desired biological function. In more detail, Opponent IV has alleged that the fusion protein would be insoluble. Claim 4a) as granted corresponds to Claim 42a) of Auxiliary Request 1.

11.116 Opponent IV is incorrect to take this view. In this regard, Claim 42a) of Auxiliary

Request 1 is dependent on any of Claims 28-29 or 35-36, which recite therapeutic uses of polypeptides having the recited biological function (inhibition of ztnf4 activity or inhibition of BR43x2, TACI or BCMA receptor-ztnf4 engagement). Thus, the fusion protein of Claim 42a) also has these biological functions. Furthermore, Opponent IV has not provided any evidence that the fusion protein of Claim 42a) would not be functional, or would not be soluble.

Claim 5c) as granted

11.117 In point 8.1.7 of the Statement of Grounds, Opponent IV has alleged that Claim 5c) of the Patent as granted lacks sufficient disclosure for the same reasons as given above with regard to Claim 4a) as granted. Claim 5c) as granted corresponds to Claims 5 and 43 of Auxiliary Request 1.

11.118 Opponent IV's objection does not apply to Claim 5 of Auxiliary Request 1, since the Claim 5 fusion proteins do not include the complete sequence of SEQ ID NO: 8.

11.119 With regard to Claim 43 of Auxiliary Request 1, this claim is sufficiently disclosed for the reasons provided above with regard to Claim 42a) of Auxiliary Request 1, on which it depends. Furthermore, Claim 5c) is also sufficiently disclosed when dependent on Claim 41 of Auxiliary Request 1, since the compounds recited in independent base Claims 27, 29, 32, 34, 36 and 40 of Auxiliary Request 1 also have the desired biological activity.

12 OVERALL CONCLUSIONS

12.1 We ask that the Oppositions be refused and that the Patent be maintained based on our Main Request (ie. the claims as granted on EP1141274); or on our Auxiliary Request 1.

13 FORMALITIES MATTERS

13.1 This Statement is filed in one complete original, accompanied by all additional documents referred to (ie. those not cited by any of the Opponents), and accompanied by 4 complete copies (including the additional documents).

13.2 Signed for and on behalf of the Patent Proprietor on 6 June 2005.

Martin R MacLean
MATHYS & SQUIRE

ANNEX 1 - LIST OF DOCUMENTS RELIED UPON

We refer to the following documents (D1-D31), which have been cited in the Opponents' opposition briefs, and to D32-D40, which are newly cited by the Proprietor.

D1	WO 98/39361
D2	WO 00/67034
D3	WO 01/12812
D4	WO 01/24811
D5	WO 98/18921
D6	EP 0869180
D7	WO 99/12964
D8	WO 98/27114
D9	Science 278: 138-131, 1997 (von Bulow & Bram)
D10	EMBO Journal, vol. 11, no. 11: 3897-3904, 1992 (Laabi)
D11	Nucleic Acids Research, vol. 22, no. 7: 1147 - 1154, 1994 (Laabi)
D12	International Immunity, vol. 10, no. 11: 1693 - 1702, 1998 (Madry)
D13	International Immunity, vol. 7, no. 7: 1093 - 1106, 1995 (Gras)
D14	WO 00/43032
D15	WO 98/55620
D16	J. Exp. Med. vol. 189, no. 11, 7 June 1999: 1747 - 1756 (Schneider)
D17	J. Exp. Med., vol. 190, no. 11, 6 Dec 1999: 1697 - 1710 (Mackay)
D18	Science, vol. 285, 9 July 1999: 260 - 263 (Moore)
D19	US 09/302,863
D20	US 60/149,378
D21	US 60/143,228
D22	US 09/255,794
D23	US 60/119,906
D24	US 60/166,271
D25	US 09/226,533 (priority document of EP 1141274)
D26	Table setting out SEQ ID NOs (provided by Opponent I)
D27	US 06/157,933

D28	J. Biol. Chem., 2003, vol. 279: 16727 - 16735 (Patel)
D29	J. Biol. Chem., 1999, vol. 274: 15978 - 15981 (Mukhopadhyay)
D30	US 5595721
D31	Alignment of human and mouse TACI (provided by Opponent I)
D32	Bodmer *et al.*, Trends in Biochem. Sci., vol. 27, No. 1, pgs 19-24
D33	Hymowitz et al., JBC vol. 280, No. 8, pgs 7218-7227
D34	Sequence alignment of "Prosite" sequence (D1) and SEQ ID NO: 10
D35	WO 02/066516 (ZymoGenetics, Inc.)
D36	Further experimental evidence concerning anti-TACI antibodies of Patent Example 18 (Proprietor's unpublished data)
D37	Xia *et al.*, J. Exp. Med., 192(1):137-143 (July 2000)
D38	Gross *et al.*, Nature 404:995-999 (April 2000)
D39	Thompson *et al.*, J. Exp. Med. 192(1):129-135 (July 2000)
D40	Gross *et al.*, Immunity 15:289,290 (August 2001)

We also refer to the following Table of Citations, which sets out – for the convenience of the Opposition Division – the documents cited by the four Opponents, the reference number ascribed to each document by the Opponents, and the Master reference number allocated to each document by the Proprietor.

Table of Citations

Citation	Opponent 3 (Genentech, Inc)	Opponent 4 (Biogen Idec Inc)	Opponent 2 (Human Genome Sciences)	Opponent 1 (Corixa Corp)	Master Ref
WO 98/39361	D1	D4	D1	D5	D1
WO 00/67034	D2				D2
WO 01/12812	D3	D6		D2	D3
WO 01/24811	D4			D3	D4
WO 98/18921	D5		D6	D10	D5
EP 0869180	D6		D7	D9	D6
WO 99/12964	D7				D7
WO 98/27114	D8	D3			D8
Science 278: 138-131, 1997 (von Bulow)	D9	D1	D2	D8	D9
EMBO Journal, vol. 11, no. 11: 3897-3904, 1992 (Laabi)	D10				D10
Nucleic Acids Research, vol. 22, no. 7: 1147 – 1154, 1994 (Laabi)	D11		D3		D11
International Immunity, vol. 10, no. 11: 1693 – 1702, 1998 (Madry)	D12	D2	D5	D7	D12
International Immunity, vol. 7, no. 7: 1093 - 1106, 1995 (Gras)	D13		D4	D6	D13
WO 00/43032		D5			D14
WO 98/55620			D8		D15
J. Exp. Med. vol. 189, no. 11, 7 June 1999: 1747-1756 (Schneider)			D9		D16

J. Exp. Med., vol. 190, no. 11, 6 Dec 1999: 1697-1710 (Mackay)			D10		D17
Science, vol. 285, 9 July 1999: 260 - 263 (Moore)			D11		D18
US 09/302,863 (Immunex Corp)			D12		D19
US 60/149,378 (Biogen, Inc)			D13	D2a	D20
US 60/143,228 (Biogen, Inc)			D14		D21
US 09/255,794 (Human Genome Sciences, Inc)			D15		D22
US 60/119,906 (Amgen, Inc)			D16		D23
US 60/166,271 (Amgen, Inc)			D17		D24
US 09/226,533 (priority document of Opposed Patent)			D18		D25
Table setting out SEQ ID NOs				D1	D26
US 06/157,933				D3a	D27
J. Biol. Chem., 2003, vol. 279: 16727 - 16735 (Patel)				D4	D28
J. Biol. Chem., 1999, vol. 274: 15978 - 15981 (Mukhopadhyay)				D11	D29
US 5595721				D12	D30
Alignment of human and mouse TACI				D13	D31

ANNEX 2

AUXILIARY CLAIM SET 1

1. Use of a compound selected from the group consisting of:
a) a polypeptide comprising the extracellular domain of BR43x2 (SEQ ID NO: 2);
b) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 2;
c) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 4;
d) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 10;
e) a polypeptide of SEQ ID NO: 4;
f) amino acid residues 8-37 of SEQ ID NO: 8;
g) amino acid residues 1-48 of SEQ ID NO: 8;
h) amino acid residues 1-37 of SEQ ID NO: 8; and
i) amino acid residues 8-48 of SEQ ID NO: 8,
for the manufacture of a medicament for treating asthma, bronchitis, emphysema, end stage renal failure, renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy, amyloidosis, or inflammation; or for inhibiting antibody production associated with an autoimmune disease, or for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation;
in a mammal by inhibiting ztnf4 activity in said mammal.

2. Use according to Claim 1, wherein said mammal is a primate.

3. Use of a compound selected from the group consisting of:
a) a polypeptide comprising the extracellular domain of BR43x2 (SEQ ID NO: 2);
b) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 2;
c) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 4;
d) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID

NO: 10;

e) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 59;

f) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 60;

g) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 20;

h) a polypeptide of SEQ ID NO: 4;

i) amino acid residues 8-37 of SEQ ID NO: 8;

j) amino acid residues 1-48 of SEQ ID NO: 8;

k) amino acid residues 1-37 of SEQ ID NO: 8; and

l) amino acid residues 8-48 of SEQ ID NO: 8,

for the manufacture of a medicament for treating asthma, bronchitis, emphysema, end stage renal failure, renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy, amyloidosis, or inflammation; or for inhibiting antibody production associated with an autoimmune disease, or for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation;

in a mammal by inhibiting BR43x2, TACI, or BCMA receptor-ztnf4 engagement.

4. Use according to any of Claims 1-3, wherein said compound is a fusion protein consisting of a first portion and a second portion joined by a peptide bond, said first portion comprising a polypeptide comprising amino acid residues 25-58 of SEQ ID NO: 2; and said second portion comprising another polypeptide.

5. Use according to Claim 4, wherein said first portion further comprises a polypeptide selected from the group consisting of:

a) amino acid residues 59-120 of SEQ ID NO: 2;

b) amino acid residues 105-166 of SEQ ID NO: 6; and

c) amino acid residues 89-150 of SEQ ID NO: 8.

6. Use according to Claim 4, wherein said first portion is a polypeptide comprising the extracellular domain of BR43x2 (SEQ ID NO: 2).

7. Use according to Claim 4, wherein said first portion is a polypeptide of SEQ ID NO: 4.

8. Use according to any of Claims 4-7, wherein said second portion is an immunoglobulin heavy chain constant region.

9. Use according to Claim 8, wherein said immunoglobulin heavy chain constant region is a human immunoglobulin heavy chain constant region.

10. Use according to Claim 9, wherein said human immunoglobulin heavy chain constant region is a human immunoglobulin heavy chain constant region of IgG1.

11. Use according to any of Claims 8-10, wherein said medicament comprises a multimer of fusion proteins.

12. Use according to Claim 11, wherein said medicament comprises an immunoglobulin heavy chain constant region that contains two constant regions and lacks the variable domain.

13. Use according to any of Claims 1-12, wherein said antibody production is associated with an autoimmune disease selected from systemic lupus erythematosis, myasthenia gravis, multiple sclerosis or rheumatoid arthritis.

14. Use according to any of Claims 1-12, wherein said renal disease is glomerulonephritis, vasculitis, nephritis or pyelonephritis.

15. Use according to any of Claims 1-12, wherein said antibody production is associated with an autoimmune disease selected from insulin dependent diabetes mellitus or Crohn's Disease.

16. Use according to any of Claims 1-12, wherein said inflammation is associated with joint pain, swelling, anaemia, or septic shock.

17. An isolated polynucleotide molecule encoding a polypeptide of SEQ ID NO: 2.

18. An isolated polynucleotide molecule of SEQ ID NO: 1.

19. An expression vector comprising the following operably linked elements:
a transcription promoter
a polynucleotide molecule according to Claim 17
a transcription terminator

20. A cultured cell into which has been introduced an expression vector according to Claim 19, wherein said cultured cell expresses said polypeptide encoded by said polynucleotide molecule.

21. A method of producing a polypeptide, comprising:
culturing a cell into which has been introduced an expression vector according to Claim 19, whereby said cell expresses said polypeptide encoded by said polynucleotide molecule; and
recovering said expressed polypeptide.

22. An isolated polypeptide having the sequence of SEQ ID NO: 2.

23. A polypeptide according to Claim 22 in combination with a pharmaceutically acceptable vehicle.

24. A pharmaceutical composition comprising:
a) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 2;
b) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 4; or
c) an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 10;
and a pharmaceutically acceptable carrier.

25. A composition according to Claim 24, wherein said antibody or antibody fragment is selected from the group consisting of:
a) a polyclonal antibody;

b) a murine antibody;

c) a humanized antibody derived from b); and

d) a human monoclonal antibody.

26. A composition according to Claim 24 or 25, wherein said antibody fragment is selected from the group consisting of F(ab'), Fab, Fv, and scFv.

27. Use of a soluble polypeptide comprising the extracellular domain of TACI for the manufacture of a medicament for treating asthma, bronchitis, emphysema, nephritis, pyelonephritis, renal neoplasms, light chain neuropathy, amyloidosis, Crohn's Disease, or inflammation associated with joint pain, swelling or septic shock in a mammal;
by inhibiting ztnf4 activity in said mammal.

28. Use of a polypeptide comprising the extracellular domain of BCMA for the manufacture of a medicament for treating systemic lupus erythematosis, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, asthma, bronchitis, emphysema, end stage renal failure, renal neoplasms, multiple myelomas, light chain neuropathy, amyloidosis or inflammation associated with joint pain, swelling, anaemia or septic shock; or for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation;
in a mammal, by inhibiting ztnf4 activity in a mammal.

29. Use of a polypeptide comprising the sequence of SEQ ID NO: 10 for the manufacture of a medicament for treating asthma, bronchitis, emphysema, nephritis, pyelonephritis, renal neoplasms, light chain neuropathy, amyloidosis, Crohn's Disease, or inflammation associated with joint pain, swelling or septic shock;
in a mammal, by inhibiting ztnf4 activity in a mammal.

30. Use of an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 6 for manufacture of a medicament for treating asthma, bronchitis, emphysema, nephritis, pyelonephritis, renal neoplasms, light chain neuropathy, amyloidosis, Crohn's Disease, or inflammation associated with joint pain, swelling or

septic shock;
in a mammal, by inhibiting ztnf4 activity in said mammal.

31. Use of an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 8 for manufacture of a medicament for treating systemic lupus erythematosis, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, asthma, bronchitis, emphysema, end stage renal failure, renal neoplasms, multiple myelomas, light chain neuropathy, amyloidosis or inflammation associated with joint pain, swelling, anaemia or septic shock; or for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation;
in a mammal, by inhibiting ztnf4 activity in said mammal.

32. Use of amino acid residues 1-166 of SEQ ID NO: 6 for the manufacture of a medicament for treating end stage renal failure, multiple myelomas, or lymphomas; or for inhibiting antibody production associated with an autoimmune disease;
in a mammal, by inhibiting ztnf4 activity in said mammal.

33. Use according to any of Claims 27-32, wherein said mammal is a primate.

34. Use of a soluble polypeptide comprising the extracellular domain of TACI for the manufacture of a medicament for treating asthma, bronchitis, emphysema, nephritis, pyelonephritis, renal neoplasms, light chain neuropathy, amyloidosis, Crohn's Disease, or inflammation associated with joint pain, swelling or septic shock;
in a mammal, by inhibiting BR43x2, TACI, or BCMA receptor-ztnf4 engagement.

35. Use of a polypeptide comprising the extracellular domain of BCMA for the manufacture of a medicament for treating systemic lupus erythematosis, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, asthma, bronchitis, emphysema, end stage renal failure, renal neoplasms, multiple myelomas, light chain neuropathy, amyloidosis or inflammation associated with joint pain, swelling, anaemia or septic shock; or for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation;

in a mammal, by inhibiting BR43x2, TACI, or BCMA receptor-ztnf4 engagement.

36. Use of a polypeptide comprising the sequence of SEQ ID NO: 10 for the manufacture of a medicament for treating asthma, bronchitis, emphysema, nephritis, pyelonephritis, renal neoplasms, light chain neuropathy, amyloidosis, Crohn's Disease, or inflammation associated with joint pain, swelling or septic shock;
in a mammal, by inhibiting BR43x2, TACI, or BCMA receptor-ztnf4 engagement.

37. Use of an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 6 for manufacture of a medicament for treating asthma, bronchitis, emphysema, nephritis, pyelonephritis, renal neoplasms, light chain neuropathy, amyloidosis, Crohn's Disease, or inflammation associated with joint pain, swelling or septic shock;
in a mammal, by inhibiting BR43x2, TACI, or BCMA receptor-ztnf4 engagement.

38. Use of an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 8 for manufacture of a medicament for treating systemic lupus erythematosis, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, asthma, bronchitis, emphysema, end stage renal failure, renal neoplasms, multiple myelomas, light chain neuropathy, amyloidosis or inflammation associated with joint pain, swelling, anaemia or septic shock; or for inhibiting effector T cells wherein said inhibition further comprises immunosuppression associated with graft rejection, graft versus host disease, autoimmune disease or inflammation;
in a mammal, by inhibiting BR43x2, TACI, or BCMA receptor-ztnf4 engagement.

39. Use of an antibody or antibody fragment that specifically binds to a polypeptide of SEQ ID NO: 18 for manufacture of a medicament for treating myasthenia gravis, bronchitis, emphysema, end stage renal failure, renal neoplasms, light chain neuropathy, amyloidosis, Crohn's Disease, or inflammation associated with joint pain or swelling;
in a mammal by inhibiting BR43x2, TACI, or BCMA receptor-ztnf4 engagement.

40. Use of amino acid residues 1-166 of SEQ ID NO: 6 for manufacture of a medicament for treating asthma, bronchitis, emphysema, nephritis, pyelonephritis, renal

neoplasms, light chain neuropathy, amyloidosis, Crohn's Disease, or inflammation associated with joint pain, swelling or septic shock;
in a mammal by inhibiting BR43x2, TACI, or BCMA receptor-ztnf4 engagement.

41. Use according to any of Claims 27, 29, 32, 34, 36 or 40, wherein said compound is a fusion protein consisting of a first portion and a second portion joined by a peptide bond, said first portion comprising a polypeptide selected from the group consisting of:
a) a polypeptide comprising amino acid residues 34-66 of SEQ ID NO: 6;
b) a polypeptide comprising amino acid residues 71-104 of SEQ ID NO: 6; or
c) a polypeptide comprising amino acid residues 25-104 of SEQ ID NO: 6;
said second portion comprising a second polypeptide.

42. Use according to any of Claims 28-29 or 35-36, wherein said compound is a fusion protein consisting of a first portion and a second portion joined by a peptide bond, said first portion comprising a polypeptide selected from the group consisting of:
a) a polypeptide comprising the sequence of SEQ ID NO: 8;
b) a polypeptide comprising amino acids residues 8-37 of SEQ ID NO: 8;
c) a polypeptide comprising amino acids residues 41-88 of SEQ ID NO: 8; or
d) a polypeptide comprising amino acids residues 8-88 of SEQ ID NO: 8;
said second portion comprising a second polypeptide.

43. Use according to Claim 41 or 42, wherein said first portion further comprises a polypeptide selected from the group consisting of:
a) amino acid residues 59-120 of SEQ ID NO: 2;
b) amino acid residues 105-166 of SEQ ID NO: 6; and
c) amino acid residues 89-150 of SEQ ID NO: 8.

44. Use according to Claim 41, wherein the first portion is a soluble polypeptide comprising the extracellular domain of TACI.

45. Use according to Claim 42, wherein the first portion is a polypeptide comprising the extracellular domain of BCMA.

46. Use according to Claim 41, wherein the first portion is amino acid residues 1-154 of SEQ ID NO: 6.

47. Use according to Claim 42, wherein the first portion is amino acid residues 1-48 of SEQ ID NO: 8.

48. Use according to any of Claims 41-47, wherein the second portion is an immunoglobulin heavy chain constant region.

49 Use according to Claim 48, wherein said immunoglobulin heavy chain constant region is a human immunoglobulin heavy chain constant region.

50. Use according to Claim 49, wherein said human immunoglobulin heavy chain constant region is a human immunoglobulin heavy chain constant region of IgG1.

51. Use according to any of Claims 48-50, wherein said medicament comprises a multimer of said fusion proteins.

52. Use according to Claim 51, wherein said medicament comprises an immunoglobulin heavy chain constant region that contains two constant region domains and lacks the variable region.

53. Use according to Claim 32, wherein said autoimmune disease is systemic lupus erythematosis, myasthenia gravis or rheumatoid arthritis.

54. Use according to Claim 32, wherein said autoimmune disease is insulin dependent diabetes mellitus, or Crohn's Disease.

55. Use according to Claim 28, 31, 35 or 38-39, wherein said renal disease is glomerulonephritis, vasculitis, nephritis or pyelonephritis.